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Sodium Metabolism
in
Health and Disease

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By

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'He shoots higher that threatens the moon, than he that aims at a tree.'

(HERBERT)

PREFACE

This monograph was written in competition for the Rogers Prize of the University of London; the closing date for entry was April, 1951. It is essentially therefore a critical review of work on sodium metabolism published up to the end of 1950. Research in this field is very active, and the more significant contributions which have since been published are referred to in a number of footnotes. The essay itself has been left as originally presented, since even a scientific monograph may aspire to some degree of unity of composition, which would be impaired by piece-meal reconstruction.

I shall not indulge myself in that species of casuistry which attempts to persuade the reader that a review of some particular field is of permanent value; for the tide of increasing knowledge makes nonsense of such pretensions. My more modest hope is that workers in this field may be directed to original publications which they may have overlooked in the maze of scientific writing; and that others of more general interests may be glad to have a review of a subject which is related to such diverse medical disciplines as biochemistry and practical therapeutics.

My interest in sodium metabolism was first aroused by reading R.A. McCance's Goulstonian Lectures. I have since had the privilege of working with him for a time, and of discussing problems with him on occasion. I take this opportunity of expressing my appreciation of his unique contribution to our knowledge of sodium metabolism.

I am greatly indebted to my chief, Professor Robert Platt, for having allowed me every facility both in the preparation of this monograph, and in research over the past few years. I have had

the advantage of many fruitful discussions with him and with other members of this unit.

I am grateful to Professors J. L. Gamble and H. W. Smith for permission to reproduce diagrams; and to Dr. R. W. Ollerenshaw and Mr. J. Kilshaw of the Department of Medical Photography, Manchester Royal Infirmary, for their help in this and other publications.

Finally, I am grateful to the University of London for awarding me the Rogers Prize, and for permitting publication of this review.

DOUGLAS BLACK.

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THE fiscal behaviour of governments is not commonly distorted by scientific prejudice; and so the prevalence of a salt tax in non-maritime countries demonstrates that the claims made for the importance of sodium in the human economy do not stem merely from the preoccupation of specialists with their own subject-matter. There is moreover a mass of more direct scientific evidence that an adequate intake of sodium is an essential of animal and human nutrition. Admittedly, simple dietary deficiency of sodium is so well compensated by diminished urinary excretion of sodium that adverse effects may be long delayed; but prolonged animal experiments have shown that a diet containing only traces of sodium is ultimately fatal (Orent-Keiles, Robinson, and McCollum, 1937). When active steps are taken to deplete the body sodium by sweating or forced vomiting, a characteristic syndrome of salt depletion quickly appears.

Any enquiry into the biological importance of sodium must be highly speculative, in view of our ignorance of intracellular metabolism, and the variations which certainly occur in the permeability of living membranes to electrolytes. On the gross chemical level, what we know of the distribution of sodium within the body enables us to assign it a prominent place in the maintenance of the volume, osmotic pressure, and acid-base composition of extracellular fluid. This type of biochemical function could be undertaken by any cation of similar valency and reactivity which did not easily penetrate into tissue cells. A rather facile explanation of the fact that it is sodium which subserves

these particular functions is that of Macallum (1926), who suggested that the extracellular fluid of mammals represents a well-preserved specimen of the Palaeozoic ocean from which their ancestors emerged. This internal milieu protects the tissue cells from the constant variation implicit in a terrestrial as opposed to a marine environment. From this point of view, the regulation of plasma sodium can be equated with the regulation of the osmotic pressure of body fluid, and it is this aspect of sodium metabolism which has been most extensively studied, and is probably of most biological importance. There are clear indications, however, that sodium does not function merely as an osmotically active cation; if that were so, it should be replaceable by potassium, which is similar to it in chemical activity, and even in atomic structure, since there are seven electrons in the outer active ring of both elements (Findlay, 1942). It is well known since Ringer's classical studies in 1883 that potassium cannot replace sodium in perfusion fluid, and that a strict balance between these two ions has to be maintained. Similar effects on cardiac action and neuromuscular irritability can be observed in the intact animal when potassium is added in excess to the bloodstream. Reactions of this type cannot be explained on an osmotic basis, and it is probable that sodium and potassium are essentially different in their relation to the electrical phenomena of polarisation at membranes. This difference could only be formulated in the language of physical chemistry, and neither the basic data nor their valid treatment are within the compass of this essay. This applies also to the possible influence of sodium in stabilising the colloidal state of body proteins, and to the effects of sodium on action potentials in the giant axon of the squid, demonstrated by Hodgkin and Katz (1949).

AMOUNT AND DISTRIBUTION OF SODIUM IN THE BODY

THE total amount of sodium in the body of a man of average size, with body weight 70 kg., is about 2,800 mEq, or 65 g. The figure of 1 g. of sodium per kg. of body weight is thus a reasonable approximation; in obese people the body fluid and sodium content are proportionately less than in men of spare habit. The physiological importance of sodium, so far as is known, derives from its relationship to other electrolytes and its osmotic effects in aqueous solution; both these are more conveniently dealt with when the amount of sodium is expressed as milli-equivalents (mEq.), rather than as milligrams (mg.). Amounts and concentrations of sodium will therefore be expressed in terms of chemical equivalence (mEq. or mM) or osmotic activity (milliosmols), the litre (L.) being used as the unit of volume. In dilute solutions such as the body fluids, sodium is present in the ionised state, so that its concentration in mEq./L. also expresses the osmotic activity due to sodium in milliosmols/L.

It is illogical to discuss the distribution of sodium in the body on an anatomical basis; it is true that the amount of sodium in different organs varies considerably, but such differences are in the main reflections of the varying fluid content of the organs. With the exception of the bones, the location of body sodium is in compartments which bear little correspondence to gross topography, as they interpenetrate the whole body. The intracellular compartment has a firm histological basis, but the extracellular compartment, the main reservoir of body sodium, is only

obvious in tissues in which it is distended by oedema. The evidence is conclusive, however, that throughout the tissues of the body there does exist a mass of fluid external both to blood-vessels and to cells, however little it may be apparent in normal tissues. In a few places, such as the lumbar theca or the anterior chamber of the eye, definite collections of this type of fluid are found; and in oedematous tissues the expanded extracellular spaces are readily seen. This extracellular fluid contains most of the sodium in the body.

EXTRACELLULAR FLUID COMPARTMENT

This includes the plasma, within the blood-vessels, and the interstitial fluid, lying between the tissue cells. The concentration of sodium in plasma is about 142 mEq./L., with a fairly narrow normal range of 5 mEq./L. on either side of the mean *. The sodium concentration in interstitial fluid is somewhat higher, about 145 mEq./L., (Darrow, 1945); this difference can be attributed to the greater 'fluidity' of interstitial fluid, which has 993 g. of water/litre, as opposed to 940 g of water/litre in plasma. For an assessment of the total amount of sodium contained in the extracellular fluid compartment, the total volume of fluid within the compartment must be determined. This problem, whose difficulties are obvious, has been approached by determining the volume of distribution within the body of various substances which were thought to be uniformly diffused through extracellular fluid, but not to enter cells. Mannitol, inulin, radio-active sodium and chloride, and sodium thiocyanate have all been used. Sodium and chloride are clearly unsuitable for absolute measurements of extracellular fluid volume, as both are known to enter cells, and sodium is also found in bone

* Sodium concentration in plasma from normal subjects has a normal distribution curve, with 80 % of values falling between 137 and 148 mEq./1., and 98 % of values between 133 and 152 mEq./1 (Wootton, King, Smith, and Haslam 1951, *Biochem. J.*, **48**, *lix.*)

in large amounts; changes in 'chloride space' are currently used in assessing gross changes in extracellular fluid volume. Thiocyanate is known to enter red blood cells, and a correction is applied for this; even so, the method gives results which are probably too high. Mannitol gives results which are sometimes much too high, and at present inulin is the substance whose volume of distribution seems to correspond most closely to extracellular fluid volume. Schwartz, Schachter, and Freinkel (1949) have studied this matter extensively; they found that the volume of distribution of inulin (inulin space) was consistently less than that of thiocyanate, radio-active sodium, or bromide, all of which are known to enter some cells. Accurate results demand a constant infusion technique, rather than a single injection of inulin, as time is needed for the inulin to diffuse uniformly through the extracellular fluid. Their results with this technique in man give an inulin space of 14 to 18 per cent of the bodyweight. This corresponds to a total of 1600 mEq. of sodium in the extracellular fluid of a 70 kg. man. Sodium is the predominant cation of extracellular fluid, amounting to about 93 % of the total base, the remainder being potassium, calcium and magnesium in amounts which are very small relative to sodium. This base is balanced by chloride, bicarbonate, sulphate, phosphate, organic acids, and by protein, as indicated in Fig. 1. The sodium in extracellular fluid seems to be present entirely as sodium ion; the loss of one electron from the sodium atom, giving it a more stable configuration, like that of the inert gas neon, may go some way towards explaining how it is that the fiery element which splutters when cast into water should become so apparently docile a constituent of our body-fluids.

The physiological importance of extracellular fluid can scarcely be exaggerated. It is the immediate environment of the tissue cells, and so it constitutes that 'milieu interne' whose fixity Claude Bernard proclaimed to be a necessary condition for the health of body cells. Constancy of composition of extracellular fluid is

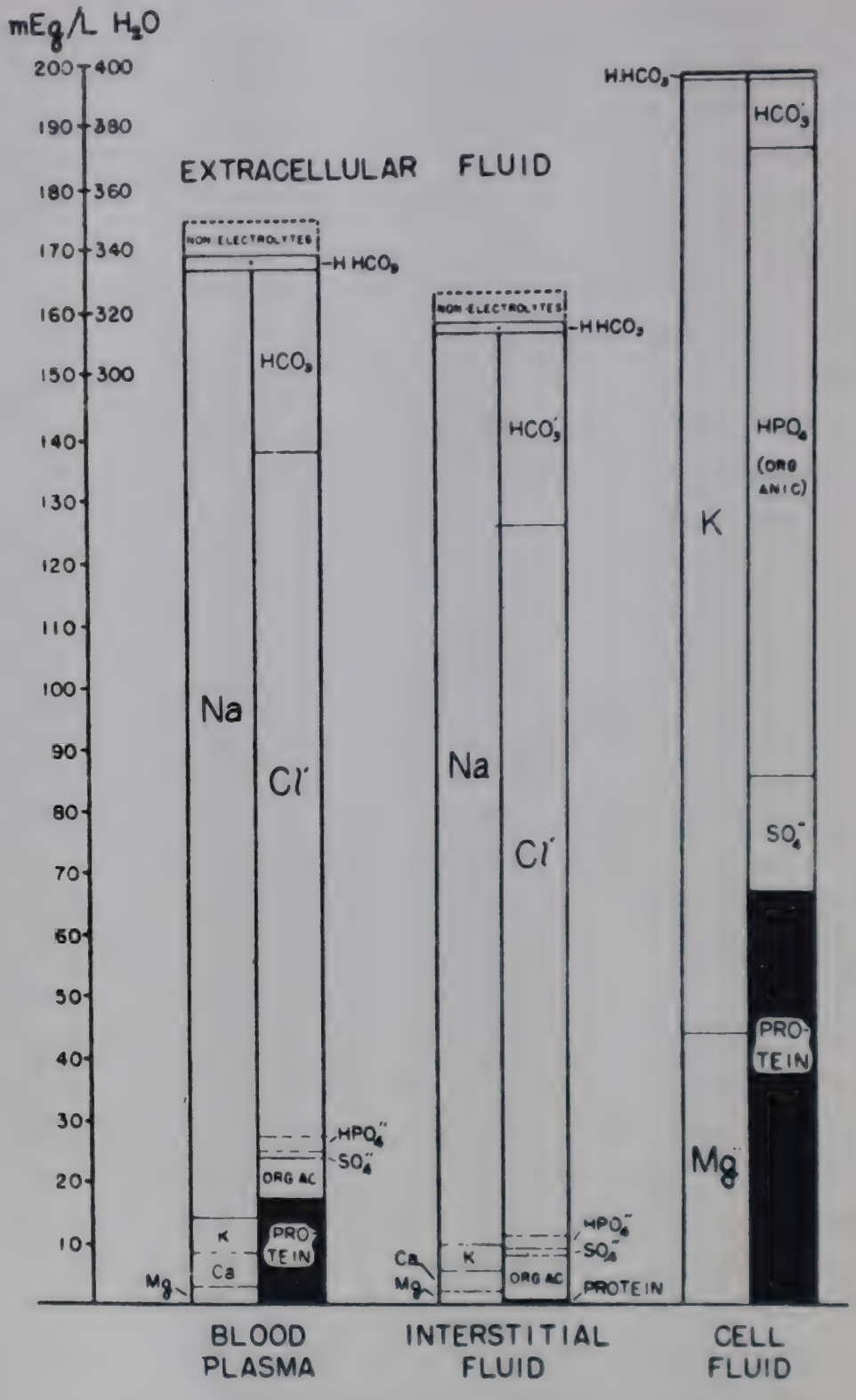

Fig. 1. Comparison of electrolyte composition of blood plasma, interstitial fluid, and cell fluid. (Gamble, 1947).

maintained at the expense of changes in volume, when necessary. For example, an injection of as much as 180 mEq. of sodium as 10 % sodium chloride within 20 minutes led to a change of only 2 mEq./L. in the plasma sodium concentration; the expected rise in plasma sodium from the addition of this amount of sodium to extracellular fluid, had no volume changes occurred, would be about 15 mEq./L. The speed with which this type of osmotic adjustment occurs in healthy people reflects the enormous size of the interfaces between plasma, interstitial fluid, and intracellular fluid. The short-term regulation of the sodium concentration of extracellular fluid is carried out mainly by a shift of water out of the cells when sodium concentration threatens to rise, and into the cells when sodium concentration is falling. Actual transfer of sodium itself into and out of the cells may also take place, but has not been demonstrated experimentally as part of the immediate reaction to threatened changes in plasma sodium concentration. The long-term regulation of extracellular fluid sodium concentration is mainly an intake-output regulation of total body sodium, but balance experiments show that shifts of sodium into and out of the cells also occur. The regulation of total body-sodium will be considered later, and the existence and availability of intracellular sodium will be the subject of the next section.

The main reason for the rather close regulation of the sodium concentration in extracellular fluid seems to be the provision of osmotic stability in body fluid. (This teleological phrasing may perhaps be excused on the plea that in health most physiological changes tend towards survival, and it would be tedious, and perhaps even unconvincing, to explain each time that no purpose lies behind such apparently purposive changes.) The contribution of non-electrolytes to the osmotic pressure of interstitial fluid, and even of plasma, is quite trivial by comparison with that of the electrolytes. Sodium, as we have seen, accounts for 93 % of the total base, so that changes in sodium concentration,

with the anion changes which would become necessary to preserve constant pH in the presence of changing sodium, will outweigh any possible changes in other bases many times. The total osmotic pressure of extracellular fluid is a little more than twice the concentration of plasma sodium in mEq./Litre. Relative changes in anions, such as chloride and bicarbonate, do not affect the osmotic pressure of extracellular fluid so long as the sodium concentration is steady; this suggests that so far as osmotic pressure is concerned, the regulation of sodium concentration is primary, and that of its associated anions secondary. Considerations of this type justify the modern emphasis on sodium rather than on chloride in studies of salt metabolism.

INTRACELLULAR SODIUM

Owing largely to difficulties in analysis, the presence of appreciable amounts of sodium within body cells has only recently been established and made the subject of intensive study. Analysis of red blood cells has shown them to contain from 4 to 16 mEq./L. of sodium (Snyder and Katzenelbogen, 1942). Direct analysis cannot however be extended to the cells of tissues other than blood, and it is these tissue cells which are of quantitative importance, as the fluid within them is more than twice the amount of extracellular fluid. Although the concentration of sodium within these cells is small, the large volume of intracellular fluid prevents the intracellular sodium from being a negligible quantity; it amounts to about 250 mEq. in a 70 kg. man, but is rather variable, as transfers of sodium between the two compartments can readily be induced. Indirect measurement of intracellular sodium can be based either on tissue analysis or on changes in sodium balance, corrected for extracellular fluid changes.

In the analysis of tissues, the specimen contains extracellular fluid as wel as cells, and the greater part of the sodium is in fact extracellular. The procedure for estimating intracellular sodium

is perforce indirect, and is based on an estimate of the extracellular fluid present in the sample; this estimate is obtained by dividing the chloride content of the sample by the chloride concentration of a calculated plasma ultrafiltrate, the correction required for intracellular chloride being very small. On the basis of the calculated amount and sodium concentration of extracellular fluid, the amount of extracellular sodium is derived, and this is subtracted from the analysed sodium content of the sample to give the intracellular sodium. Although this type of method may seem umpromising as a source of accurate results, there is substantial agreement between independent groups of investigators as to the sodium concentration in intracellular fluid. Darrow (1945) gives figures mainly based on rat tissue. Although there is some difference in the sodium concentration of intracellular fluid derived from rat liver, brain, cardiac and skeletal muscle, the preponderance of skeletal muscle in the soft tissue weight makes it permissible to use the figure of 7 mEq./L. of cell water, derived from muscle analysis, as an approximation to the sodium concentration of intracellular fluid in general. Figures of the same order were obtained by Mudge and Vislocky (1949) in human muscle obtained at biopsy.

Changes in intracellular sodium may also be assessed indirectly from changes in sodium balance. In this type of study, change in extracellular fluid volume is estimated from the chloride balance and the concentration of chloride in extracellular fluid. The expected change in sodium balance can then be derived from the sodium concentration of extracellular fluid, and the estimated change in extracellular fluid volume. This expected change in sodium balance is compared with the actual change, and any discrepancy is taken as a measure of intracellular sodium gain or loss. The various balances on which this estimate is based are corrected for observed changes in the plasma values of chloride and sodium; a change of 1 mEq./L. of plasma sodium is the equivalent of a change of 12 to 15 mEq. n

sodium balance. Since the error of the method for plasma sodium is $\pm$ 2 mEq./L., this last correction is somewhat artificial, unless the conditions of the observations are such as to involve really gross changes in plasma sodium. A further possible source of error is change in the sodium of bone, and this may be controlled to some extend by observing the calcium balance. This type of assessment of changes in intracellular sodium is more applicable to observations in man than the method of tissue analysis, which would involve repeated biopsy of muscle. In animal experiments, the two types of method give results which are in general agreement, and when all allowance is made for the indirect calculations and the error of the basic data it is fair to conclude that sodium is present in the cells, and that variations of quantitative significance can be induced therein. (Elkinton, Winkler, and Danowski, 1948; Darrow and Pratt, 1950).

Independent evidence of the entry of sodium into cells comes from studies with radio-active sodium. It has already been mentioned that injected labelled sodium has a volume of distribution which is greater than that of inulin. Moore (1949) has studied the time relations of the fall in radio-active sodium concentration in plasma adter a single intravenous injection. Equilibrium within a volume of body fluid corresponding to most estimates of extracellular fluid volume is attained within an hour. Thereafter there is a definite further fall in sodium concentration, greater than can be accounted for by urinary excretion during the relevant time; this must represent penetration of radio-active sodium into the cells, and possibly into bone. During the first few hours at least, the increase in sodium space is more probably explained by entry into cells than by active incorporation in the mineral part of bone.

SODIUM IN BONE

Although sodium forms only a small proportion of bone ash,

being present in the proportion of 1 mole of sodium for every 30 moles of calcium, the total mass of electrolyte in the skeleton is such as to make the sodium of bone amount to about a third of the body sodium. It is thus considerably greater in amount than the intracellular sodium, but less than the sodium of extracellular fluid. The relative amounts in a 70 kg. man are of this order:

Extracellular fluid	1600	mEq.
Intracellular fluid	250	„
Bone	900	„

It is unlikely, however, that sodium in the calcified matrix of bone is available to body fluids, and it is usual to neglect transfers of sodium to and from bone, unless there is evidence of very rapid bone formation or resorption. In acute observations on sodium metabolism, the sodium of bone can be neglected; in more extended observations, a correction of sodium balance could be made on the basis of the sodium: calcium ratio in bone. The amount of such a correction would be very small, and no experimental evidence to support its use has been obtained.

MEMBRANE PERMEABILITY TO SODIUM

Many membranes of the body are obviously freely permeable to sodium; the presence of sodium both inside and outside the capillary wall in substantially the same concentration, and the ubiquity of sodium in body secretions, make this clear. On the other hand, the great disparity in sodium concentration between extracellular and intracellular fluid has suggested that the cell wall may oppose a barrier to the passage of sodium. In early formulations, such as the brilliant disquisition of Van Slyke (1926) on the factors governing electrolyte distribution in body fluid, it was assumed that the cell wall was impermeable, both to sodium and potassium. Conway (1945) assumed that the cell

wall was permeable to potassium but not to sodium, pointing out that the hydrated sodium ion is larger than the hydrated potassium ion in a ratio of 1.5. : 1. On this assumption, he was able to show that the concentration differences of sodium between extracellular and intracellular fluid were such as to satisfy the requirements of osmotic and Donnan equilibria between these fluids, and also to give a calculated value for the membrane potential across the cell wall which was in good agreement with the observed value. He was careful to note that a continuous active extrusion of sodium from cells would have the same effect in producing a concentration difference as would an impermeability of the cell membrane to extracellular sodium. In a later review, Conway, (1947) accepts the accumulated evidence for an active process of sodium extrusion, but considers that differential permeability of the cell wall to sodium and potassium is still of biological importance, since active sodium extrusion is a process limited by the energy available for its performance. On this view, the amount of sodium outside the cells is greater than that inside partly because the cell wall is less freely permeable to sodium than to potassium, and partly because an active sodium extrusion is going on to a limited extent. Measurements of sodium outflow from frog muscle cells, using radio-active sodium, give a value which would require 50 calories/hr./kg. of muscle, if all the outflow were due to active transport (Ussing, 1949); since the resting metabolism of this tissue is about 175 calories/hr./kg., sodium extrusion could theoretically be covered by the energy available, but it is unlikely that so high a proportion as 30 % of available energy would in fact be used for this purpose. Ussing believes that other mechanisms, such as exchange diffusion, may be concerned.

In summary it may be said that the presence of sodium inside body cells, and some degree of permeability of the cell wall to sodium, are generally admitted, mainly as a result of convincing

studies with labelled sodium; but the relative permeability of the cells to sodium and potassium, and the mechanisms by which a difference in sodium concentration is maintained across a permeable membrane, are still the subject of much discussion and experiment.

REGULATION OF BODY SODIUM

In health, the sodium content of the body is kept within fairly narrow limits, and in a temperate climate the urine is the only important channel of sodium excretion. It is therefore possible by estimating the salt content of a day's urine to gain approximate information on the daily intake of sodium. Such studies, for example that carried out by Ashe and Mosenthal (1937) on the urines of a thousand citizens of New York, show a considerable individual variation. Although only 5 % of their subjects excreted less than 4 g. of salt, and only 1.6 % more than 20 g., the scatter of salt intakes between 4 and 20 g. was considerable. It is also a matter of common observation that individuals add rather variable amounts of salt to their food. To some extent this individual variation seems related to the potassium content of the food taken. Vegetables are richer in potassium than animal foods, and more salt is used in cooking and at table, when vegetables form a large part of the diet. Similarly, ordinary bread is baked with salt to an average concentration of 1 % NaCl, and specially prepared salt-free bread is unpalatable. Salt hunger is more notable in the herbivora, with their 'salt licks', than in carnivora. In man, some craving for salt is observed, especially after a period on a salt-free diet, but the wide normal range of dietary intake of salt suggests that this is determined largely by chance and custom, and that the fine biological regulation of the sodium content of the body must be sought elsewhere. In support of this view, artificial variation in salt intake to levels above and below the normal

range is well compensated by the regulation of sodium excretion; similar mechanisms would be well able to deal with the quite considerable variation in sodium intake found spontaneously. Another observation which suggests that regulation of intake is not crucial in determining sodium balance is that profuse sweating may lead to salt deficiency without arousing a spontaneous craving for salt; there seems to be a real difference here between salt and water regulation, for a comparable deficit of water leads to unbearable thirst. Moreover, Adolph (1943) has shown that animals which have been deprived of water so as to incur a water deficit will drink the appropriate amount to restore the deficit, when water is again presented to them, and will stop drinking when the deficit has been made good. No such precision of adjustment of salt deficit by salt intake has ever been observed, and the main regulation of body sodium seems to be by changes in excretion. This control is obviously very effective, as it can maintain approximate constancy of the body sodium at widely variable levels of intake.

Besides variation in dietary intake, variation in the loss of salt through the skin will tend to alter the sodium content of the body. The loss of salt in the sweat is not a part of the regulating mechanism for body sodium, for it is determined not by the need to lose or conserve salt, but by the need for maintaining body temperature within narrow limits. Sweating is a tax on sodium regulation, and not a means of maintaining it. The loss of sodium by sweating may be considerable in a hot climare, or even during severe physical exertion in a temperate climate. The concentration of sodium in sweat is 50—100 mEq./L., about half that in blood; the loss of water therefore exceeds that of salt, but it commonly happens that thirst leads to replacement of the water, but not necessarily of the salt, so that there is not only a loss of salt from the body, but also a fall in the sodium concentration in body fluid, instead of a rise, which would be the expected effect of loss of sweat without

fluid replacement. The absolute loss of sodium from the body may be considerable, as a litre or more of sweat may be formed in an hour, so that an average day's intake of 400 mEq. of sodium could be dissipated in six hours by sweating alone. It is true that part of the process of adaptation to hot climates is a lowering of the salt concentration in sweat (Dill et al., 1933); there is some evidence that the salt concentration in sweat is controlled by the adrenal cortex, and may even be used as a measure of desoxycorticosterone (DCA) — like activity (Conn, 1949). However, the economy of sodium which can be effected in this way is limited, and in practice copious sweating always leads either to voluntary increase of salt intake, or to action of the renal mechanisms of sodium conservation. In health it may be said that dietary intake of salt and the amount of sweat formed are variable, and that the renal output of sodium is adjusted to maintain the sodium content of the body in spite of this variation.

RENAL HANDLING OF SODIUM

In treating this subject, we shall assume that renal function is best described by a filtration-reabsorption hypothesis, that sodium can be reabsorbed in both the proximal and the distal tubule, and that direct excretion of sodium by the tubules does not occur to any appreciable extent. Many determinations of glomerular filtration rate (GFR) in man, using the clearance of inulin, mannitol, thiosulphate, or allantoin, give a value around 120 ml./min., with variation from 90 to 150 ml./min. This very large volume of fluid is differentiated in its passage through the tubule to form urine which has a minute volume usually of less than 5 ml./min., and a composition very different from that of the original glomerular filtrate. Direct analysis of glomerular filtrate suggests that it has the composition of a protein-free ultrafiltrate of plasma, so that the glomerular capillary wallacts as a simple filter; the work needed to separate off the filtrate

against the colloid pressure of plasma proteins is derived, as in other capillaries, from the fall in hydrostatic pressure, and so ultimately from the heart-beat, and the kidney itself does no work in this part of the process. At a GFR of 120 ml./min, and a plasma sodium concentration of 140 mEq./L., the amount of sodium filtered per minute will be about 17 mEq./min., neglecting the small opposing error from the protein content of plasma, and from the Donnan effect on sodium concentration in the two phases. On the other hand, the sodium excretion per minute varies usually between 0.05 and 0.5 mEq./min., so it is clear that much the greater part of the filtered sodium is reabsorbed, just as by far the greater part of the water filtered is reabsorbed. In the course of an average day, no less than 24,000 mEq. of sodium are filtered, but the urinary output is likely to be only about 500 mEq./day or less; similarly, from a daily filtration of 170 litres of water, only 1—2 litres of urine are formed.

Superficially, it may seem rather an odd arrangement that so much fluid is filtered to make so little urine, but extensive internal circulation of fluid seems to be rather a favourite biological mechanism; the secretion and reabsorption of intestinal juices, and the continuous circulation of tissue fluid are both processes of similar magnitude. A high GFR is obviously necessary in organisms whose tubules do not secrete urea and similar metabolites, if a high clearance of such substances is needed. Moreover, the high ratio of filtered sodium to excreted sodium offers possibilities for the fine regulation of sodium output which we must now examine in more detail.

As a basis for discussion, we may take Homer Smith's current views on the mechanism of sodium excretion (Wesson et al., 1948, Smith, 1950a.)*. His scheme for the tubular reabsorption of sodium and water is indicated in Fig. 2, from Wesson et al., (1948), and his theory is well summarised in the caption to this figure:—

* See also H. W. Smith 'The Kidney', New York, 1951.

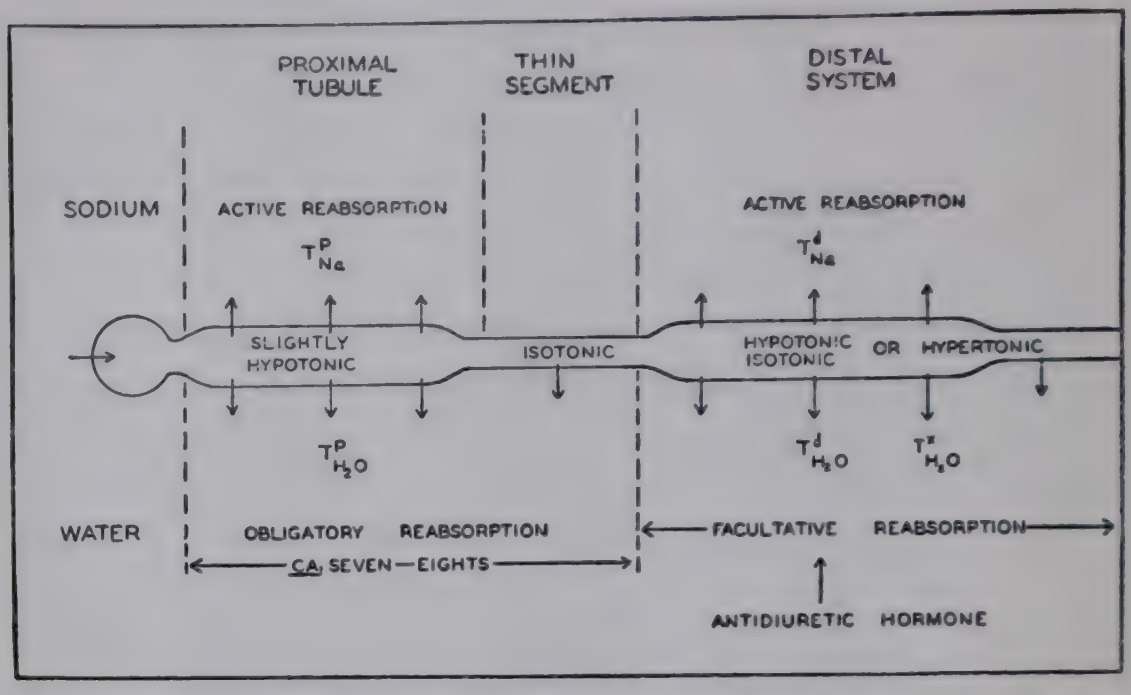

Fig. 2. Diagram to illustrate Homer Smith's views on sodium excretion — for explanation see text. (Wesson et al., 1948).

"In the hypothesis presented in this paper it is presumed that sodium with chloride and bicarbonate is reabsorbed in the proximal tubule by an active process, leading to the formation of a slightly hypotonic urine. In consequence of this hypotonicity water diffuses back into the plasma so that a fluid essentially isotonic with plasma is delivered to the distal tubule. It is conceived that the function of the thin limb is to promote osmotic equilibration. Reabsorption in the proximal tubule and thin limb accounts for roughly seven-eighths of the glomerular filtrate, leaving one-eighth to be operated upon in the distal tubule.

It is believed that water and sodium are actively but independently reabsorbed in the distal tubule by processes which are limited by maximal rates (T^{d}_{m} H_2O and T^{d}_{m} Na). The distal reabsorption of water is activated by the antidiuretic hormone which, with the osmoreceptors of the supraopticohypophyseal system, comprises the mechanism for the control of water equilibrium."

Sodium reabsorption in the proximal and distal segments of the tubule is rather different, in that the proximal tubule reabsorbs a constant *proportion* of the sodium presented to it by the glomerulus, whereas the distal tubule reabsorbs all the sodium presented to it up to a certain *amount*, the remainder spilling over into the urine. It is obvious that such a mechanism could account for variations in sodium excretion induced by variations in sodium load in the glomerular filtrate; but before discussing the practical consequences of the theory we may notice the type of evidence on which it is based.

Since the glomerular filtrate is presumably a fluid of the same general nature as tissue fluid, which is itself in equilibrium with cell fluid, it may be conceded that transfer of sodium from the tubule fluid to the tubule cells is either an active process, or the accompaniment of an active transfer of other substances, especially water. The suggestion that sodium is actively reabsorbed and that water follows it passively, seems to be based on the occasional finding by Walker et al. (1914) that the fluid obtained by puncture of the proximal tubule may be hypotonic, although it is usually isotonic with respect to sodium; Homer Smith suggests that in most cases the rapidity with which water is reabsorbed in the proximal tubules from a solution made hypotonic by active sodium reabsorption makes it difficult to demonstrate the original lowering of sodium concentration by active reabsorption, and he admits that the evidence so far as active sodium reabsorption is concerned is not conclusive. There is rather firmer evidence that the tubule fluid as it leaves the proximal tubule, or rather the loop of Henle, in which the final proximal water reabsorption occurs, is essentially isosmotic with plasma; this conclusion is based on experiments in dogs in whom an osmotic diuresis was induced by mannitol, the diuresis being of such intensity that the urine volume amounted to 65 % of the filtered water. Under these highly abnormal conditions, it was thought that the urine so rapidly formed might not be in con-

tact sufficiently with the distal tubule cells to be appreciably modified by their action, and might therefore approximate to the fluid leaving the proximal segment of tubule; it was found that the urine was essentially isosmotic with plasma, and in so far as urine formed under these peculiar conditions is representative of fluid leaving the proximal segment of tubule, such fluid may also be assumed to be isosmotic.

In the nature of the case, it is hard to get direct evidence for the separation of tubular sodium reabsorption into two distinct processes, one in the proximal segment plus Henle's loop, the other in the distal tubule. It is worth mentioning, therefore, that the morphology of the proximal tubule and Henle's loop would be suitable to an active process of sodium reabsorption in the proximal segment, accompanied by most of the associated water, the final equilibration being made in the loops of Henle which in their close relation to the vase recta at least present the appearance of a dialysing machine (Shannon, 1942). Other active reabsorption processes, as for glucose, protein, and amino-acids, have been located in the proximal tubule (Oliver, 1948, 1950), and it is this part of the nephron which undergoes hypertrophy when the number of nephrons is artificially reduced (Oliver, 1945). Microchemical methods have not been employed to study the site of sodium reabsorption in dissected nephrons, but Oliver (1950) has shown that the proximal convolutions contain the highest amount of mineral ash in micro-incinerated specimens, both from normal rats and rats treated with calciferol.

These considerations make it seem likely that an isosmotic fluid with about the same sodium concentration as plasma enters the distal part of the tubule. Unfortunately, as Oliver points out, the phrase 'distal tubule' may be taken to mean either the distal convoluted tubule, or else merely that part of the tubule distal to Henle's loop, and including not only the convoluted tubule, but also the collecting and junctional tubules. No attempt has been made to apportion the remaining part of sodium and

water reabsorption between these parts of the tubule, but the phenomenon of 'pyelovenous return' observed by radiologists shows that the collecting ducts cannot simply be left out of account. We shall therefore use the phrase 'distal tubule' to include not only the distal convolution, but also the collecting system. Given the entry of a fluid not differing greatly from plasma in its sodium concentration, it is obvious that the formation of urine with a sodium concentration lower than that of plasma will require either active reabsorption of sodium, or secretion of water. The second possibility is unlikely, and it is generally accepted that the formation of urine of low sodium concentration must have included a process of active sodium reabsorption.* Homer Smith locates this partly in the distal tubule, and also suggests that the distal tubule transfer of sodium has an upper limit — the T^d_m Na in his terminology — which is analogous to that used for maximal tubular transport of diodrast or glucose — T_m diodrast or T_m glucose, qualified by the indes 'd' to indicate that only the distal tubule is being considered. The upper limit of distal sodium transfer is set by the energy available for carrying it out.

What proportion of the total sodium reabsorption goes on in the proximal and in the distal tubule? In water diuresis and in diabetes insipidus, so long as the osmotic pressure of plasma is not artificially raised, the volume of urine excreted does not exceed an eighth of the water filtered at the glomerulus. The puncture experiments of Walker et al. (1941) showed that the concentration of creatinine increased during passage down the proximal tubule at a rate which would suggest that about seven-eights of the filtered water was reabsorbed in the proximal

* It is possible that a process of secretion of water by the distal tubule might form a hypotonic urine with less energy expenditure than a process of solute reabsorption. This aspect of „negative anomalous osmosis" is fully discussed by Brodsky and Rapoport, 1951, *J. Clin. Invest*, **30**, 282.

From a study of water diuresis in renal failure, Platt and Roscoe (work to be published) believe that water secretion can be demonstrated.

tubule. Homer Smith suggests that so far as water is concerned, seven-eights of the reabsorption goes on in the proximal tubule, and is 'obligate', while the rest of the water is available for 'facultative' reabsorption, which is active when antidiuretic hormone is present, but can be inhibited when pituitary antidiuretic activity is absent as in water diuresis or diabetes insipidus. If this proportion is accepted for water reabsorption, and if the fluid leaving the proximal tubule is in fact of a sodium concentration similar to glomerular filtrate, it will follow that $\frac{7}{8}$ of filtered sodium will be reabsorbed proximally, leaving $\frac{1}{8}$ to be handled by the distal tubule. It may be noted that although much the greater part of the sodium is absorbed proximally, the reabsorption here proceeds along with water reabsorption, and it is only in the distal tubule that sodium need be absorbed in high concentration as compared with plasma; it is of interest that Ljungberg (1947) found that the chloride concentration in the cells of collecting tubules was much higher than that in the cells of the cortex. Further evidence which may possibly bear on the proportion of sodium reabsorbed in the distal tubule has been obtained by Duggan and Pitts (1950) from a study of the action of very high doses of mercurial diuretics in dogs. They found that the proportion of sodium reabsorption which was inhibited by mercury increased with the mercury dosage, but only up to a limit, which could not be transcended by further increasing the dose of mercury. This limit of what one might call (mercury-inhibitable-reabsorption) was about 13—15 % of the control level of sodium reabsorption, s figure which agrees well with the 12.5 % postulated by Homer Smith for the distal component of sodium reabsorption. Duggan and Pitts suggest that at maximal dosage a complete inhibition of distal sodium reabsorption is probably present, though they cannot exclude the less likely possibility that there are two components in proximal tubule sodium reabsorption, one of which is inhibited by mercury and is by chance equal to the reabsorption usually attributed to the distal tubule.

Summarising, there is fair evidence that about $\frac{7}{8}$ of the filtered sodium (sodium load) is reabsorbed, probably by an active process, in the proximal tubule; the remaining $\frac{1}{8}$ of sodium load is presented to the distal tubule, which is thought by Homer Smith to have a limited capacity for absorbing sodium. This capacity is of the order of $\frac{1}{8}$ of an average sodium load so that at low sodium loads the sodium will be completely reabsorbed, while at high sodium loads the excess sodium presented to the distal tubule will escape reabsorption. It is of interest that a somewhat similar theory has been arrived at independently by Kruhoffer (1950) from work mainly done on the rabbit, an animal which is unsuitable for some types of renal work because of the exceptional variability of GFR in this species (Smith, 1947).

Application of Homer Smith's theory to the observed facts of sodium excretion

In some respects, this theory is well fitted to explain the process of sodium excretion. For example, the fall in sodium excretion which occurs when the plasma sodium is low can well be attributed to a fall in the filtered load of sodium, such as to bring the amount of sodium presented to the distal tubule well below the capacity of that segment of the tubule to reabsorb sodium. Similarly, a fall in glomerular filtration rate, such as occurs in cardiac failure, will also reduce the filtered load of sodium, and the low sodium excretion in cardiac failure has been attributed to this mechanism (Mokotoff et al., 1948). On the other hand a raised GFR or a raised plasma sodium are often associated with increase of sodium excretion; for example, injection of hypertonic saline, which increases both GFR and plasma sodium to some extent, increases the sodium output in normal people. The theory places the whole emphasis on change in filtered load of sodium as the determinant of ultimate sodium excretion. In many circumstances, it is not possible to determine whether this is so, as variations in GFR which might materially increase or

decrease the filtered load cannot be measured with any certainty. We would suggest that the theory as it stands is incomplete, in that it makes insufficient allowance for variability in tubular function, and we will now bring forward some examples of change in sodium output which seem not to depend on demonstrable change in either GFR or plasma sodium, and which must therefore be attributed to change in tubular handling of the sodium load.

Black, Platt and Stanbury (1950) have drawn attention to one such instance. They induced low levels of sodium excretion by putting normal subjects on a low-sodium diet for some days, and then raised the filtered load of sodium artificially by injection of hypertonic saline. Although the excretion of sodium increased slightly, it did not approach the level of sodium excretion found in the same subjects on a normal diet, even although the filtered load of sodium was higher than in the normal person. This seems to be a clear demonstration of an increased activity of the tubules in reabsorbing sodium, induced by spending a few days on a salt-poor diet.

Again, when normal people are made to hyperventilate, the excretion of sodium in the urine is very considerably increased, although there is no corresponding increase in the filtered load of sodium. The injection of desoxycorticosterone acetate (DCA) is associated with a fall in the excretion of sodium, although no change in filtered load can be detected. Moreover, the well marked diurnal variations in sodium output cannot be accounted for by the very small observed changes in filtration rate during sleep (Sirota et al., 1950), and are probably also reflections of change in tubular handling of sodium.*

These phenomena suggest that tubular reabsorption of sodium is potentially variable, and the low output of sodium on a salt-

* Extended observations on the mechanism of diurnal variation in sodium excretion are now available in the paper of Stanbury and Thomson, 1951, *Clin Sci.*, **10**, 267.

deficient diet, even with a high artificial sodium load, suggests that a maximum limiting value for T_dNa is unlikely. Homer Smith suggests that a limit of this kind is necessary on thermodynamic grounds, but it is known that the oxygen consumption of the kidney is many times greater than would correspond to the energy requirement for the osmotic work which the kidney normally performs; this makes a thermodynamic limit on renal tubular performance less likely. Admittedly, the total osmotic performance of the kidney seems to be limited, in that high solute excretion leads to an osmotic diuresis rather than to further increase in urinary concentration; but the osmotic work required in reabsorbing sodium, even with an increased sodium load, is less than that involved in the concentration of urea. The very large amounts of sodium which can be reabsorbed under special conditions, as in the experiments of Black, Platt and Stanbury, also suggest that the process of sodium reabsorption is not limited by the capacity of intermediate substances in a transfer mechanism such as is concerned for example in glucose reabsorption.

Stimulus and mechanism in changes of sodium output

In so far as sodium output is determined by changes in sodium load, two possible stimuli present themselves — change in plasma sodium, and change in plasma volume. Change in plasma sodium would increase or decrease the sodium load directly, and the mechanism of change in sodium output could then be that postulated by Homer Smith. Change in plasma volume is likely to be associated with change in renal blood flow and GFR, and this has sometimes been demonstrated experimentally. Expansion of the plasma volume by rapid plasma infusion increases the renal blood-flow and GFR (Wilson and Harrison, 1950); on the other hand, the low plasma volume of shock or of salt depletion is associated with a diminished GFR. It is of interest to note that the increase in sodium output after albumin infusion

in patients with cirrhosis is not closely related in time or degree to the observed increase in GFR (Luetscher et al., 1950); conversely, the low GFR found in shock is not uniformly associated with a low output of sodium. These examples in disease of lack of correlation between sodium load and sodium output may serve to amplify those we have already given from the physiological field.

Alteration in the filtered load of sodium can be considered as influencing the ultimate sodium output fairly directly, but the variation in sodium output attributable to changes in tubular action is less wel defined in regard to both stimulus and mechanism One possibility which has to be considered is that the efficiency of tubular reabsorption might be modified by purely mechanical factors related to urine flow. At high rates of urine flow, tubular reabsorption might be less efficient either because of a faster flow of fluid past the tubule cells, or by dilatation of the tubules so that an 'axial stream' might fail to come into effective contact with the tubule cells. In the isolated perfused kidney, Winton (1937) was able to show that high rates of filtration were associated with high chloride excretion; but the evidence on the effect of increasing urine volume in man is less definite. Mach (1946) claims that water and alcohol diuresis materially increased the urinary output of salt, and remarks with Gallic humour that it is not by chance that we find salted biscuits on the bar tables. On the other hand, Eggleton and Smith (1946) found a lowered output of chloride in water diuresis. When a diuresis is induced not by water but by infusing osmotically active substances, the results are equally conflicting. For example, Wesson and Anslow (1948) found that mannitol diuresis in the dog is attended by an increased output of sodium, while McCance et al., (1944) found a fall in sodium output with urea diuresis in dehydrated men, though not in normal men. Mercurial diuresis is of course associated with a greatly increased output of sodium, but here a direct action on the reabsorption process in the tubule

cells is certainly present, and any mechanical effect of the diuresis is trivial in comparison. On the whole, the mechanical effect of an increased urine flow does not seem to be critical in causing increased sodium output, as it can readily be offset by other factors.

It has also been suggested (Trueta et al., 1947) that at different times the blood passing through the kidney may perfuse different sets of nephrons; the cortical nephrons would be likely to absorb sodium more effectively than the nephrons nearer the medulla, which are said to have less convoluted tubule. Homer Smith (1950*b*) has criticised this theory at length, and we agree with his conclusion that there is no evidence that this type of process is of any importance in the physiology of the human kidney.

This leaves us, so far as the tubules are concerned, with changes in the activity of the transfer mechanism from the tubular lumen through the cell into the interstitial fluid of the kidney. Sodium transfer is likely to be related at least in part to the mechanism of base exchange which Pitts (1948) has shown to be responsible for the regulation of urinary acidity. Pitts has located this process in the distal tubule, and it seems reasonable to place the variable component of sodium reabsorption in the same segment. (We are here using 'variable' in a rather special sense, to differentiate the 'obligate' reabsorption in the proximal tubule, which is proportional to sodium load, from the 'facultative' reabsorption in the distal tubule, which we conceive to be 'variable' by endocrine and possibly other action on the tubule cells.) The intimate biochemistry of sodium transfer in this region has not yet been studied, though the tissue culture work of Taggart and Forster (1950) on phenol red transfer in the proximal tubule suggests a way of approach. The evidence for a variable component of sodium transfer has therefore still to be based on observed changes in sodium excretion, which has the limitation that other possible variables such as sodium

load have to be controlled before the evidence can be accepted.

We have already given some examples of variability in sodium output which seems to be determined by changes in tubular activity. The stimulus to enhanced tubular reabsorption of sodium may be either a low level of plasma sodium, or a diminished extracellular fluid volume, and we have already seen that either of these causes a diminished filtered load of sodium. This could in itself account for a falling off in sodium excretion, so evidence of change in tubular reabsorptive activity is only admissible from experiments in which the filtered load was measured as well as the output. The observations of Black et al., (1950) and of Weston et al., (1950) satisfy this requirement, but it is not possible to discriminate between low plasma sodium and low extracellular fluid volume as the effective stimulus to enhanced tubular reabsorption activity, since both these occur as a consequence of salt depletion. Diminished reabsorption of sodium, in relation to load, occurs in alkalosis induced by hyperventilation (Stanbury, 1950), and here the stimulus appears to be change in blood pH, or in CO_2 tension.

The mechanism of changes in tubular handling of sodium is obscure. When there is a profound change in the internal environment, as in hyperventilation, a direct action on the tubule cells is quite likely, and the change in sodium reabsorption may be conditioned by the requirements of the Pitts ion — exchange mechanism. In mild salt deficiency, which produces a very large increase in tubular reabsorption of sodium, the plasma sodium level may be little different from normal, and a direct action of the stimulus on tubule cells seems less likely. The well-known fact that patients with Addison's disease and adrenalectomised animals continue to excrete large amounts of sodium even when the plasma sodium is low suggests that the adrenals are a necessary part of the mechanism for conserving sodium; and they must act on the tubules, since the filtered load of sodium is less

than normal in Addison's disease, and thus cannot account for the enhanced sodium excretion.*

Relation of adrenal activity to sodium excretion

The influence of the adrenals on sodium excretion can best be studied in the adrenalectomised animal or the patient with Addison's disease, so far as defect is concerned; and excess can be studied in normal people treated with adrenocorticotrophic hormone (ACTH), or in patients with Cushing's syndrome. The ready availability of synthetic DCA has caused much confusion, as it is doubtful whether synthetic DCA has any physiological counterpart, and the very existence of a special group of 'mineralo-corticoids' can reasonably be called in question. Perhaps the most critical difference between synthetic DCA and the effect of natural adrenal hormones is that DCA is salt-retaining at all levels of plasma sodium, except possibly in Cushing's syndrome, whereas cortical extracts are salt-retaining at low levels of plasma sodium, but may actually enhance the output of salt when the plasma sodium is raised (Woodbury et al. 1950). This does not affect the value of DCA as a therapeutic agent in Addison's disease, where the plasma sodium is low, but it does suggest that the physiological action of adrenal hormones on salt excretion is something other than a DCA-like effect, as suggested by Leaf and Couter (1949).

When adrenal hormones are deficient or lacking, there is an increased output of sodium in the urine, even when the plasma sodium is low. Tubular reabsorption of sodium is depressed, since the amount of sodium filtered is less than normal, so that in the absence of altered tubular function one would expect a low rather than a high output of sodium. The abnormality of tubular function is completely reversible by cortical extract or

* On re-reading this section on the renal regulation of sodium, I am struck once more by the disparity between the efficiency of this renal activity and our limited knowledge of it, and can only exclaim. Les reins ont ses raisons, dont la raison ne connaît point'.

by DCA. On the other hand, in Cushing's syndrome there is an increase in plasma sodium in some cases, though this is the exception rather than the rule (Soffer, 1948). When retention of sodium is present in Cushing's syndrome, it is usually associated with a low plasma potassium and chloride, the alkalosis being related to the low plasma potassium (McQuarrie et al., 1937). The fact that the plasma sodium is not constantly raised in Cushing's syndrome does not in itself imply that tubular handling of sodium is usually normal, as retention of sodium could be masked either by reduction in intake, or by expansion of the extracellular fluid volume. Kriss and Futcher (1949) found that three patients with the syndrome excreted chloride to the same extent as normal controls; with salt loading, the patients had a larger sodium and chloride diuresis than the controls, suggesting that sodium reabsorption is not greater than normal in Cushing's syndrome. There is an apparent discrepancy between the well-established fact that adrenal deficiency leads to loss of sodium in the urine, and the few observations which suggest that excessive spontaneous adrenal activity is not generally associated with sodium retention. This is the more surprising, as Conn (1949) has shown that the high sodium content of sweat in Addison's disease finds its counterpart in a low sodium content of sweat in Cushing's syndrome. The observations on sweat would suggest that the salt-retaining adrenal steroids are increased in Cushing's syndrome, but that so far as the urine is concerned, their action is overborne by another factor. This may possibly be the increased output of potassium in Cushing's syndrome, for potassium diuresis is known to increase the rate of excretion of sodium. The effect of stimulation of the adrenal cortex in normal man by ACTH has been studied by Forsham et al. (1948) and others; there is a marked retention of sodium during the first few days of ACTH administration, and a corresponding increased output of sodium when the hormone is discontinued. However, the more prolonged experiments of Bartter et al. (1950) suggest that

the sodium retention produced by ACTH is transient, even when hormone administration is continued. In summary, there is good evidence that in man a deficiency of adrenal cortical activity leads to a profound failure of sodium reabsorption by the renal tubule; but the converse effect of excessive adrenal activity, spontaneous or induced by ACTH, is much less definite. Increased sodium reabsorption has been observed, but only as a rather transient phenomenon, at least under normal dietary conditions of sodium intake. It has not been shown in man that the prolonged increase in sodium reabsorption observed on a low-sodium diet is due to increased adrenal cortical action, though it appears quite possible.

In the rat, Deane et al., (1948) have shown that dietary restriction of salt is associated with hypertrophy of the zona glomerulosa of the adrenal gland, and that the administration of DCA leads to atrophy of this zone. On the other hand, ACTH administration leads to hypertrophy of the zona fasciculata, and hypophysectomy to atrophy of this zone. If this observation were applicable to man, it might explain why the effects of ACTH and Cushing's syndrome on sodium excretion are so indefinite by comparison with those of DCA. Another possibility is that increasing amounts of hormone act on the tubule cells in a fashion which can be represented by a logarithmic curve; if this were so, the effect of the hormone in hormone-deficient subjects would be very striking, but in normal subjects it would be small and difficult to establish.

The adrenals seem to be the endocrine glands most clearly involved in the regulation of sodium excretion. There is some evidence that androgens and oestrogens can produce sodium retention, and that posterior pituitary hormone can under certain circumstances induce sodium excretion *; but the physio-

* We have recently re-examined the effect of posterior pituitary extract on sodium output, using 24-hour periods to eliminate the effect of diurnal variations; in these experiments, there was no significant change in sodium output. (Black and Thomson, 1951, *Clin. Sci.*, *10*, 511).

logical importance of these other endocrine effects on sodium excretion has not been established.

So far we have considered the amount and distribution of sodium in the body, and some at least of the agents which effect sodium balance. It remains to notice internal shifts of sodium under physiological conditions, before discussing some of the distortions of sodium metabolism met with in disease.

INTERNAL CIRCULATION OF SODIUM

THERE are several processes now to be considered which are associated with very large internal shifts of sodium; in health they do not affect the sodium balance, but they are of great importance in disordered sodium metabolism, because of the large amounts of sodium involved. They are the secretion and reabsorption of sodium in the alimentary tract, the exchange of sodium between plasma and interstitial fluid, and that between interstitial and intracellular fluid.

THE ALIMENTARY TRACT

In the normal course of digestion, large amounts of digestive secretions of varying salinity are secreted into the alimentary tract. Gamble (1947) gives a total of 8,200 ml. for a 24-hour period, made up thus:

Saliva	1500 ml.
Gastric secretions	2500 ml.
Bile	500 ml.
Pancreatic juice	700 ml.
Succus entericus	3000 ml.

Figure 3, taken from Gamble, shows the usual composition of some of these secretions, and it is apparent that very large amounts of sodium are involved. Only gastric juice, the secretion of the peptic glands, has a low sodium concentration; and this is always partially neutralised by gastric mucus, which has, like the other secretions, a sodium concentration rather higher than that in plasma. The total daily secretion of sodium into the

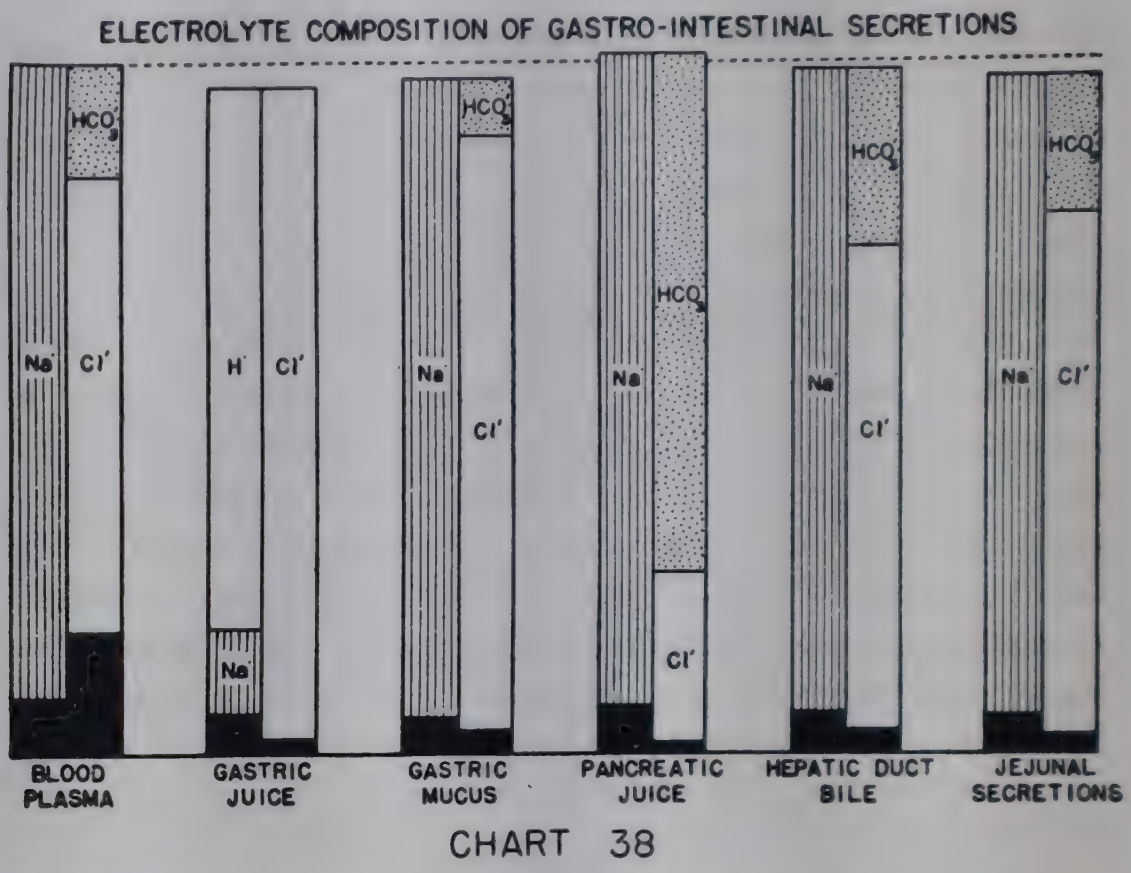

Fig. 3. Electrolyte composition of gastro-intestinal secretoins. (Gamble, 1947)

alimentary tract amounts to about 1000 mEq., and this, together with the 100—300 mEq. of sodium in the diet, is almost completely reabsorbed, for the sodium content of normal stools is negligibly small. The process of sodium reabsorption in the bowel has not been much studied, but Visscher et al. (1944) have shown by the use of radio-active sodium that it is an active process, in which shifts of sodium may take place against a concentration gradient. The low salinity of stools in itself would indicate that at least the terminal stage of sodium reabsorption must be active.

PLASMA AND TISSUE FLUID

The principles of fluid exchange between plasma and tissue fluid were enunciated by Starling (1909). The hydrostatic pressure of blood inside the capillaries tends to force fluid out from

the capillary to the tissue spaces; this tendency is opposed by the osmotic pressure of the plasma proteins, to which the capillary wall is not freely permeable. At the arterial end of the capillary, the hydrostatic pressure is greater than the colloid osmotic pressure, and fluid leaves the capillary; at the venous end of the capillary, the hydrostatic pressure has fallen, and the proteins have become concentrated, so that the colloid pressure now exceeds the hydrostatic pressure, and fluid flows in the opposite direction, from tissue space to within the capillary. The fluid involved in this shift contains sodium, and the rapidity of diffusion of labelled sodium testifies to the magnitude of this inner circulation of sodium. Diffusion of labelled sodium thoughout the extracellular space is a matter of minutes, as might indeed be expected from the very large total area of the capillary bed.

There is perhaps only one respect in which Starling's concept has to be modified in the light of subsequent work. The physicochemical equilibrium which he postulated between plasma and tissue fluid is of course fundamental, and remains valid; but more importance would now be attached to physiological alterations in the capillaries themselves. Zweifach and Kossmann (1937) showed that there were two types of capillary circulation — a rapid circulation at high pressure, which would favour filtration of fluid, and a slow circulation through tortuous channels at low pressure, which would favour reabsorption. The predominant type of capillary circulation can be modified by humoral agents, and the possibility of nervous control has not been excluded. This work makes it less possible to predict the effect of changes in cardiac output or in venous pressure on the balance of fluid exchange in the tissues, as local alterations in capillary circulation may occur to modify the effects of general circulatory changes.

TISSUE FLUID AND CELLS

The evidence for the presence of sodium in tissue cells has

already been reviewed. Although experiments with radio-active sodium show that the sodium exchanges with intracellular as well as with extracellular sodium, the rate of turnover is much slower. Darrow (1950) regards the slowness of changes in intracellular sodium as evidence that these changes represent a biological change differing in mechanism from the rapid physicochemical exchanges between plasma and interstitial fluid. It can certainly be said that the amount of sodium undergoing transfer across the cell walls in unit time is small by comparison with the rapid transfers of sodium in the alimentary tract and across the capillary membrane. Although the total amount of sodium in the cells changes only slowly, rapid changes in concentration may occur as the result of transfer of water into and out of the cells. Apart from this, changes in intracellular sodium concentration and amount seem to have been observed in potassium deficiency, when sodium may partly replace potassium inside cells; and in metabolic alkalosis and acidosis, when intracellular sodium parallels the changes in plasma bicarbonate (Darrow, 1950). As already mentioned, the internal shifts of sodium of this type are small in rate and amount by comparison with those found between different collections of extracellular fluid.

SODIUM METABOLISM IN INFANCY

Before concluding the review of normal sodium metabolism, it is necessary to mention the special problems which attend the first few months of life. It is not an accident that our knowledge of sodium metabolism owes much to investigations made by paediatricians such as Gamble or Darrow; for the exchanges of water and salt are more rapid in infancy, and states of water and salt deficiency are a more urgent problem in infants than in adults. Water exchange in the infant is 3—4 times as rapid as in the adult. As Gamble (1947) says, 'It is therefore not surprising that the mechanisms of control of extracellular fluid volume operate with less precision in the infant than in the adult, and

permit larger oscillations in day to day body weight referable to change in water balance'. These remarks refer directly to water exchange, but sodium is equally concerned in the maintenance of extracellular fluid, and the sodium metabolism of infants is correspondingly unstable. A young infant takes about a pint of milk daily, containing 10 mEq. of sodium; this is rather a low amount by comparison with an average adult intake of sodium of 200 mEq./day, for a young infant has a higher proportion of extracellular fluid than an adult. A low salt intake is quite appropriate in health, for the infant's kidneys are unable to concentrate salt to the same degree as the adult kidney (McCance, 1948). In disease, however, the infant's low salt intake makes him vulnerable to salt depletion when abnormal losses occur; and at the same time, the low capacity of the kidney for eliminating salt makes him vulnerable to salt excess when parenteral saline is given in too large amount. For these reasons, sodium balance in infancy is even less secure than in the adult.

ABNORMALITIES OF SODIUM METABOLISM

A NUMBER of syndromes have been recognised which can be related to alterations in sodium metabolism. Each of these syndromes is encountered in many different disease states, yet so far as sodium metabolism is concerned the natural history and effects of the syndrome are similar, even though the pathogenesis may be widely different. For example, salt depletion in Addison's Disease and in gastro-enteritis may be similar, though the cause in each case is completely different. It is therefore justifiable in considering abnormal sodium metabolism to devote most attention to a few general syndromes, rather than to discuss in detail the alterations of sodium metabolism which occur in specific disease states.

Abnormal sodium metabolism cannot be considered without respect to concurrent changes in water metabolism, and in the anions which balance sodium in body fluid. Sodium depletion is not one syndrome, but several, according to whether water is depleted less or more than sodium, or to the same extent; and it may also be modified by changes in chloride, bicarbonate or potassium ions. The same generalisation applies to sodium excess. In both, the concentration of sodium in extracellular fluid is at least as important in determining the clinical picture as is the absolute amount of sodium in the body. Leaving aside for the present alterations in acid base balance, we can distinguish four primary syndromes of abnormal sodium metabolism;

1. Sodium depletion with water depletion.
2. Sodium depletion without water depletion.

3. Sodium excess with water excess.
4. Sodium excess without water excess.*

This austerely biochemical classification may well conceal the frequency and clinical importance of these syndromes, so it may be well to state that they correspond in general to the clinical syndromes:

1. Dehydration secondary to salt depletion.
2. Water intoxication, 'miners' cramps'.
3. Generalised oedema.
4. Dehydration secondary to water depletion.

The first two syndromes have sodium depletion in common, and the second two sodium excess; so it will make for economy of treatment if we discuss the causes of salt depletion and of excess first, and later describe how the effects of these states are modified by concurrent water depletion and excess.

CAUSES OF SODIUM DEPLETION

In theory, sodium depletion could arise either because of an inadequate intake of sodium, or because of excessive losses of sodium. In actual practice, inadequate intake of sodium can be dismissed as a primary cause of clinical sodium depletion, though it may aggravate the effects of abnormal losses of sodium. The mechanisms for conserving sodium are effective in preventing sodium depletion of any clinical importance on a diet which is virtually sodium-free. Abnormal sodium loss can occur in the sweat, in the urine, by vomiting and by diarrhoea, and from gastro-intestinal fistulae; some degree of sodium loss is also associated with haemorrhage and the exudation from burnt areas and wound surfaces, but it is not of clinical importance by comparison with haemoglobin and protein loss.

Sweat is a hypotonic solution, in the sense that the sodium

* Somewhat similar classifications of disordered sodium metabolism have been proposed by Gastineau, 1950, *Proc. Mayo Clinic*, **25**, 630, and by Conway, Lee and Sykes, 1951, *Postgrad. Med. J.*, **27**, 434.

concentration therein is only about half that in plasma; so that the effect of simple sweating is to deplete body water to a greater extent than sodium. However, when water and other non-saline fluids are drunk in response to the thirst occasioned by copious sweating, the water balance is corrected without a corresponding replacement of sodium. The presence of sodium depletion without a corresponding water depletion is associated clinically with cramping of the muscles (miner's cramps), an acute phenomenon readily curable by saline drinks. The syndrome of 'heat exhaustion' in the tropics probably represents the same biochemical state, of more gradual onset; the plasma sodium is lowered in this syndrome (Ladell and Waterlow, 1944), suggesting that water depletion is either absent, or of less degree than the sodium depletion.

Abnormal loss of sodium in the urine may be associated with renal tubular failure due to renal disease, with failure of the adreno-cortical control of sodium output, and with some types of diuresis. In renal disease, excessive loss of sodium is rather uncommon; even in chronic renal failure with polyuria, the capacity of the tubules to reabsorb sodium seems rarely to be impaired. There is, however, a syndrome of 'salt-losing nephritis', described by Thorn et al. (1944), in which large amounts of sodium are lost in the urine. In this syndrome, the giving of DCA does not prevent the loss of sodium in the urine; the tubules themselves are unable to reabsorb sodium normally, and it is not a question of failure of adreno-cortical control. In Addison's disease, there is a similar abnormal loss of sodium in the urine, but here the defect can be corrected by the use of DCA. Both 'salt-losing nephritis' and Addison's disease are rather rare conditions, though of much theoretical interest; abnormal losses of sodium in the urine are usually associated with polyuria, notably in diabetes mellitus. The mechanism of sodium loss in polyuria is not well understood. In water diuresis, although there may be a small initial loss of sodium, this is not

maintained, and water diuresis cannot be regarded as an important cause of sodium loss; in diabetes insipidus, which is the pathological equivalent of a sustained water diuresis, there is no sodium depletion. In an osmotic diuresis, when the increase of urine flow is a response to the increased excretion of a solute, the case is rather different. In a normally hydrated person, the effect of osmotic diuresis is to increase both the concentration and excretion rate of the loading solute; the concentration of other solutes is diminished, but to a less extent than the urine flow is increased, so that the excretion of other solutes in unit time is increased. Brodsky et al. (1950) have shown that this type of process can account for the urinary sodium loss in diabetes; they increased the urinary excretion of glucose by intravenous injection, and found that sodium loss in the urine increased, and was related to urine flow. The same effect could be produced by loading solutes other than glucose, such as urea. The increased sodium loss in osmotic diuresis stands in interesting contrast to the effective conservation of sodium in water diuresis and suggests that in these clinical conditions of polyuria where sodium is lost in the urine, the diuresis is of the osmotic type. This generalisation does not of course apply to the polyuria of renal failure, in which sodium loss is inconstant. A rather different cause of abnormal sodium loss in the urine, which also has to be considered in diabetic patients with ketosis, is the excretion of fixed anions in the urine; these may be neutralised by base, including sodium, but with normal kidneys this loss of fixed base is soon checked by the substitution of ammonia for fixed base. When the kidneys are abnormal, with defective ammonia formation, continued acidosis can lead to serious sodium depletion (Gamble, 1947). Sodium depletion by the urinary route may also arise in the course of regimes designed to combat sodium excess. Schroeder (1949) has emphasised the dangers of combining mercurial diuresis and a low-salt diet in the treatment of congestive heart failure. The predominant action of mercurial

diuretics is to inhibit the reabsorption of sodium, probably in the distal tubule (see p. 24). On a low salt diet, the excretion of sodium in response to mercurials may greatly exceed that of water, and produce a relative sodium depletion, associated with diminished plasma and extracellular fluid volume. The consequent impairment of renal circulation may then cause renal excretory failure, associated with urea retention and an oliguria which no longer responds to mercurial diuretics. Sulphanilamide also diminishes sodium reabsorption, and has been used in the treatment of cardiac oedema (Schwartz, 1949); its use probably carries the same risks as are associated with mercurial duiretics in patients on a Kempner rice diet, or other low-salt regime.

In health, the excretion of sodium in the stools amounts to about 5 mEq./day (Shohl, 1939); this amount is very small both in comparison with the total excretion of sodium, and with the large amount of sodium, over 1000 mEq./day, which has entered the gut and been reabsorbed. Vomiting and diarrhoea both cause considerable loss of salt, for the sodium secreted into the alimentary tract escapes reabsorption to a greater or less extent. When equal amounts of fluid are lost, diarrhoea is a more potent method of sodium depletion than vomiting, in view of the high sodium concentration in intestinal as opposed to gastric secretion; but both vomiting and diarrhoea are among the commonest clinical causes of sodium depletion. Leakage of gastro-intestinal secretions from fistulae is uncommon, but gastric and intestinal suction can lead to large losses of sodium which must be corrected by parenteral administration of saline fluids.

CAUSES OF SODIUM EXCESS

Just as a low intake of sodium does not in itself cause significant sodium depletion in man, so a high ingestion of sodium is not in itself a sufficient cause of sodium excess. If the daily intake of salt is increased to 30 g. a day, some of the added salt is retained, but this phenomenon is not of clinical importance,

and is quickly reversed when the salt intake returns to normal. The amount of salt needed to cause oedema, in the presence of normal salt excretion, is such as to provoke vomiting or diarrhoea when given rapidly by mouth. The only context in which high sodium intake may be of clinical significance as a cause of sodium excess in the body is the parenteral use of saline infusion; here the rough and ready defence of an outraged alimentary tract is by-passed, and excessive amounts of sodium can be given in this way. Even so, it is doubtful whether oedema would be readily produced by saline infusion in persons whose powers of excreting sodium were unimpaired by disease. The response to the injection even of hypertonic saline in normal people is a prompt increase in urinary sodium output, sufficient to eliminate any ordinary intravenous load of sodium.

It follows that we must seek the cause of clinical sodium excess in an impaired excretion of sodium. The amount of sodium normally excreted in sweat and in the stools is very small, so significant sodium excess implies a diminished output of sodium by the kidneys. This is not to say that the kidneys must themselves be diseased, or even that they must be impeded in their function by unfavourable conditions of bloodflow; it is just as likely in many cases that the kidneys are functioning normally, but that the regulating mechanism which promotes the renal response is at fault. For example, the oedema of acute nephritis can reasonably be ascribed to renal disease producing a retention of sodium; it is also possible to argue that the oedema of heart failure is caused in part by a defective blood-flow to the kidhey; but the sodium excess of Cushing's syndrome, of DCA overdosage, of hepatic cirrhosis, of the pre-menstrual period, or of massive inflammatory oedema, can not be related either to renal disease or to changes in the blood-flow to the kidney.

The excretion of sodium is of course dependent on the formation of urine, so that any patient with urinary suppression is liable to sodium excess, unless his intake of sodium is curtailed.

This applies not only to the urinary suppression of renal tubular necrosis, but also in some degree to the oliguria associated with deprivation of water. In men whose water intake is minimal, the urine volume falls to 500 ml. per day or less, and the excretion of solutes in this small volume of urine is severely limited. To some extent, urea can be said to compete with sodium and its associated anions for the small amount of available 'osmotic space' in the urine. In healthy subjects at least, some kind of compromise occurs, with a high urinary concentration both of urea and sodium; but at the same time the total elimination of both sodium and urea is less than is needed for balance, so that the concentration of both sodium and urea in the body increases (Black, McCance and Young, 1944). Whether there is an actual excess of sodium in the body, or merely an excess of sodium relative to water, depends on whether the intake of sodium during the period of water deprivation is high or low. Possibilities of sodium retention similar to those seen in men experimentally deprived of water obviously arise in patients whose water intake is prevented by any cause, or whose losses of water are enhanced by fever, without any corresponding increase in intake.

Suppression of urine from kidney disease, or from primary water deficiency in the body, can account for very few of the sodium retentions observed clinically. Adrenal overaction or DCA overdosage is a rare cause of sodium retention, and it is also known that oestrogens promote sodium retention. The tendency to sodium retention which follows surgical operations has been related by Hardy (1950) to adrenal overaction, but further evidence is needed. Hardy merely observed a depression of the eosinophile count coincident with the sodium retention but Eliel and others (1950) have since reported a post-operative tendency to potassium loss and metabolic alkalosis, reminiscent of the electrolyte changes in the adrenal overaction in Cushing's syndrome.

Any state of clinical oedema must involve a positive salt

balance, whether or not the salt retention is primary, or only secondary to some quite different process which compels a water retention, and so a lowering of the sodium content of extracellular fluids, which can in itself be a stimulus to sodium retention. The relationship between sodium and water retention may well be different in the different clinical types of oedema; the causes of oedema in renal disease and in cardiac failure may be discussed here, not so much with the hope of explaining these types of oedema as of illustrating the difficulties which attend attempts at explanation. Similar difficulties beset the applied physiologist who tackles the oedema of hepatic disease, of inflammatory disease, or even of varicose veins; but we will confine this discussion to 'renal' and 'cardiac' oedema, as they perhaps best exemplify the interplay between renal and extrarenal factors in sodium retention.

Sodium retention in renal disease

It is a striking clinical fact that oedema is rare in advanced chronic renal failure, while it is the rule in the early stages both of Type I and of Type II nephritis (Ellis, 1942). In renal disease at least, it is impossible to ascribe sodium retention to a lowering of glomerular filtration, for oedema is characteristically absent when the GFR is very low (terminal nephritis), and present when the GFR is normal (most cases of early Type II nephritis), or only slightly reduced (acute Type I nephritis). The net excretion of sodium depends on a balance between sodium filtered by the glomeruli, and sodium reabsorbed by the tubules. In oedematous types of nephritis, tubular reabsorption of sodium is normal or even increased; later on, tubular reabsorption is diminished, more sodium is excreted, and oedema disappears. The diminution in sodium reabsorption is coincident with impairment of the power to concentrate urea, and it is tempting to ascribe both changes to tubular failure, This may not be the only operative change, however, as the filtration pressure in the

surviving glomeruli is also increased, and this would in itself tend to diminish sodium reabsorption (Platt, 1948).*

The oedema of acute Type I nephritis is not unlike that which may be produced in a normal person by the ingestion over a period of excessive amounts of salt. Volhard put forward the concept of a pre-renal deviation of salt and water, but it seems fairly clear that there is haemodilution in this type of nephritis, as judged by serial haemoglobin estimations and estimations of plasma volume (Cardozo, 1946: Roscoe, 1950). The participation of the plasma in the oedema makes it more likely that we are dealing with a renal retention of salt and water, rather than with an abnormal leakage of fluid from the blood into the tissues. The plasma sodium is normal in acute Type I nephritis, but the sodium clearance is low, which again favours a renal cause for the salt retention. An analysis of the relative importance of changes in glomerular and in tubular function on promoting sodium retention in acute Type I nephritis has not been made, and the exact mechanism of sodium retention is quite obscure.

In Type II nephritis, the position is rather different. The oedema is massive, quite beyond anything that could be produced in a normal person by salt loading. The haemodilution which is so characteristic of acute Type I nephritis is lacking in Type II nephritis, except in so far as a true anaemia is present (Roscoe, 1950). The sodium excretion is certainly very low in Type II nephritis, but here the plasma sodium is often low, and it is possible that the low salt output is a renal response to the low plasma sodium, and not a sign of a primary alteration in renal handling of sodium. Orloff et al. (1950) found that when concentrated albumin solution was infused into patients with 'ne-

* It is also possible that the raised blood pressure of chronic renal disease may contribute to increasing sodium output. When perfusion pressure is increased in experimental animals, the sodium output rises, and this has been ascribed to a rise in intrarenal pressure impeding tubular reabsorption of water and solutes (Selkurt, 1951, *Circulation*, **4**, 541).

phrosis' some of them showed an increase in sodium excretion; when this happened, it was preceded by an increase in the sodium concentration of plasma, suggesting that the primarily low sodium concentration in plasma may have been responsible for the low pre-infusion excretion of sodium. Volhard's theory of a prerenal deviation of salt and water is obviously more tenable in Type II than in acute Type I nephritis, and the hypoproteinaemia of Type II nephritis presents itself as the obvious cause of leakage of fluid from the capillaries. The story cannot be simplified to make hypoproteinaemia solely responsible for the oedema of Type II nephritis, however, for sudden changes in the urine output of salt and water may occur without change in the plasma proteins, and oedema may be lost while the plasma proteins remain low (Roscoe, 1950). Extrarenal factors are more important in the oedema of Type II nephritis than in that of Type I nephritis, but Type II nephritis is likewise a renal disease, and the discrepancy between plasma protein levels and the degree of oedema is probably due to changes in the renal handling of sodium. Again, an analysis of the relative importance of changes in GFR and in tubular function is lacking.

Sodium retention in cardiac failure

The classical explanation of cardiac oedema is that the raised venous pressure of heart failure is communicated at least to the venous end of the capillaries, and favours transudation of fluid from the bloodstream to the tissue spaces (Fishberg, 1940). The concept of 'backward failure' was challenged by Warren and Stead (1944), who claimed that the primary event in heart failure was not a rise in venous pressure, but a fall in cardiac output; this leads to a diminished circulation of blood through the kidneys, which would favour a primary salt retention by the kidneys. This view has been supported by the observations of Merrill (1946) and of Mokotoff et al. (1948) who found a low renal blood flow and GFR in patients with congestive heart failure,

and claimed that this was the cause of the retention of sodium which is generally admitted to occur in heart failure, and must indeed be present to permit expansion of the extracellular fluid volume. This view of the pathogenesis of congestive heart failure, with its emphasis on the kidney and on sodium, has not gone unchallenged. Peters (1948) pointed out that Starling's analysis of the factors governing filtration of fluid from the capillaries was based on inescapable principles of physical chemistry, and that the rise in venous pressure could not be summarily dismissed, as the 'forward failure' school tends to do. He also criticised the use of dye methods for determining plasma volume, in the presence of hepatic engorgement, since an abnormal loss of dye bound to protein might well occur in the hepatic capillaries, which are rather permeable to protein; this would cause an inflated estimate of plasma volume, and the results of dye methods could not be used to exclude the initial diminished plasma volume required by the 'backward failure' theory. Peters (1950) again claims that the oedema of heart failure can be explained by the working of Starling's principle, and by the effect of the loss of fluid into the tissues in diminishing plasma volume, and so stimulating the adrenocortical mechanism for conserving sodium. It has also been found that a rise of pressure in the renal vein in dogs is associated with diminished sodium excretion (Blake et al., 1949), even when there is no change in renal blood flow or GFR; this observation suggests that renal activity in cardiac oedema may be affected by circulatory changes other than those implied in the concept of 'forward failure'. The concept that sodium retention by the kidneys is the primary cause of cardiac oedema is difficult to reconcile with the finding of Schroeder (1950) that the concentration of sodium in plasma and extracellular fluid is often low in patients with cardiac oedema.

These criticisms of the 'forward failure' theory do not affect the important observations that sodium excretion is reduced in patients with cardiac oedema, and that the glomerular filtration

is often low, even in the type of heart failure with a high cardiac output which is associated with anaemia or chronic emphysema. They do, however, suggest that the generalisation of Starling (1909) that oedema is seldom due to a single cause is illustrated, and not contradicted, by the oedema of heart failure. In assessing the relative importance of renal and extrarenal factors, single observations on patients with established oedema are of comparatively little value, as raised venous pressure and a low cardiac output are usually both present. An attempt at a more dynamic approach has been made by Brod and Fejfar (1950), who made continuous observations of heart output, venous pressure, renal blood flow and GFR, and urinary output of water and chloride in patients with heart failure before and during spontaneous diuresis. The only change which they found consistently related to a rise in urine-flow was an increase in renal blood flow and GFR; venous pressure and cardiac output did not change materially. Studies on the shock syndrome (Lauson et al., 1944) have shown that there is a mechanism which cuts down renal blood flow when cardiac output is reduced, and the proportionate fall in renal blood flow is much greater than that in cardiac output. The observations of Brod and Fejfar suggest that this mechanism may operate with variable intensity in cardiac failure, and the variations may account for some of the changes in sodium excretion. Unfortunately, the collection of observations of this type involves much discomfort to the patient, and the rise in renal blood flow and urine output which they observed may have been due partly to the patient becoming accustomed to their multiple procedures.

Although the mechanism of sodium retention in cardiac failure is controversial, the importance of sodium retention is clearly shown by the therapeutic success of measures aimed at circumventing it, the use of mercurial diuretics and a low-sodium diet. Some patients show a poor response to mercurial diuretics, and in these it is probable that haemodynamic renal factors are more

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important than in those patients who respond well to mercurial diuretics. These probably act on the distal tubule, and if the GFR is greatly depressed, so little sodium may ever reach the distal tubule that a satisfactory sodium diuresis may fail to happen.

We have now reviewed some of the causes of sodium depletion or excess in the body. Before dealing with the syndromes related to these changes, it must be pointed out that the effects of change in body sodium are profoundly modified by concurrent changes in water balance. In other words, an abnormal concentration of sodium in extracellular fluid is at least as important as the absolute amount of sodium in the body in determining the clinical picture of abnormal states of sodium metabolism. To give a concrete example, a man deprived of water on a low-sodium diet may have a deficit of sodium in the body, but his water deficit will be proportionately greater, and he will have a raised concentration of plasma sodium; his tissue cells will be dehydrated just as they would be in a state of sodium excess without an equivalent water excess such as may be produced by injection of hypertonic saline. In either situation, he feels thirst, and the osmotic pressure of his body fluids is higher than normal, though in one situation his total body sodium is less, and in the other greater than normal. For this reason, we must take the state of water balance into account in describing the effects of abnormal sodium balance.

1) SODIUM DEPLETION WITH SIGNIFICANT WATER DEPLETION

This is the syndrome described by Marriott (1950) as 'salt depletion', and is probably the commonest clinical type of body fluid depletion. The possible causes of sodium depletion have already been discussed, and we must now consider the effects of sodium depletion which is not artificially modified by a high intake of watery fluid. In this syndrome, some water is lost as a necessary part of the process of sodium loss, since sodium is

always eliminated in solution. More important, a loss of sodium must imply either a fall in sodium concentration in extracellular fluid, or a fall in the amount of extracellular fluid; in actual fact, both these changes are found in established salt depletion. The shrinking of the extracellular fluid makes some water available for excretion, and at the same time the fall in plasma sodium removes the physiological stimulus to the production of pituitary antidiuretic hormone, so that a water diuresis is likely. This can be observed in normal people during the first day or two on a salt-poor diet; it is less notable clinically, partly because the developing period of the sodium deficiency may not be closely observed, and partly because in many of the clinical causes of salt depletion the loss of water is roughly equivalent to that of salt, and the water lost in this way is not available for urinary excretion. The fall in extracellular fluid volume may not be entirely accounted for by external loss of water; a fall in plasma sodium indicates a fall in the osmotic pressure of the extracellular fluid, and this would favour the passage of water from the extracellular fluid into the cells. Such a shift of water has been demonstrated by Darrow and Yannet (1935) in experiments in which sodium depletion, without loss of water, was induced in dogs and rabbits by injecting glucose solution intraperitoneally, and later removing an equal volume of fluid into which sodium had diffused. Analysis of muscle showed an increase in the intracellular fluid phase. As already mentioned, in clinical salt depletion there is usually a considerable external loss of water, so the absolute volume of intracellular fluid maty not be increased, but there is still a dilution of the intracellular fluid corresponding to that indicated by the lowered sodium concentration of extracellular fluid. In salt depletion, the main burden of fluid loss therefore falls on the extracellular fluid phase, which includes the plasma volume.

This selective depletion of the extracellular fluid phase is a cardinal feature of sodium depletion, and many of the charac-

teristic changes can be traced to it. The fall in plasma volume predisposes to peripheral circulatory failure, with a low cardiac output and diminished circulation to the peripheral tissues. This lessening of superficial blood flow accounts for pallor of the skin, and the blood flow through the skin may be insufficient for heat loss to go on in the normal way, so that 'dehydration fever' may appear in the absence of other cause for pyrexia. The diminution in extracellular fluid may be obvious, with looseness of the skin, and lowered intra-ocular pressure. The blood-pressure is often low, but this is not invariably so, for McCance (1936) found a normal blood-pressure in severe experimental sodium deficiency. A normal blood-pressure cannot be taken to mean a normal plasma volume, however, for Grant and Reeve (1941) have reported that the blood-pressure in air-raid casualties with indubitable low plasma volume may be normal or even raised, owing to strong vasoconstrictor response to a diminished cardiac output; this is more common in young people, with normal arterioles.

Whether the constriction of vessels is adequate to maintain blood-pressure or not, it does have important effects on kidney function. Even in McCance's experimental sodium deficiency, with a normal blood-pressure, there was clear evidence of impaired renal function, and the GFR, as assessed by sucrose and creatinine clearances, was low. The retention of urea is well marked, and seems to be related more to the diminished supply of blood to the kidneys than to any intrinsic renal defect; the kidneys can form a urine of normal specific gravity, with 3 or more per cent of urea. It is not surprising that the effective output of urea is largely dependent on GFR, for about half the urea filtered is normally excreted, in contrast with the 1—2 % of filtered sodium; the tubules obviously differentiate the glomerular filtrate to a much less extent with regard to sodium, and it is generally held that no active tubular process is concerned in the handling of urea, but that about half the urea is reab-

sorbed passively along with water, in the direction of the osmotic gradient for urea. A significant fall in GFR diminishes the amount of urea which is available for excretion; there is no compensating refusal of the tubule cells to accept the passive reabsorption of urea along with water, and in conditions of oliguria, often found in advanced sodium depletion, the proportion of urea reabsorbed is even increased. By contrast to their essentially neutral attitude to urea, the renal tubules in sodium depletion reabsorb sodium with unusual activity (Black et al., 1950). The daily output of sodium is greatly reduced, and potassium becomes the predominant cation in the urine. The low output of sodium in the urine may persist in spite of what is normally a powerful stimulus to increased sodium excretion. McCance (1936) found that the urinary excretion of sodium induced by the alkalosis of voluntary hyperventilation was much less in sodium-depleted than in normal people. The diuretic response to a given water-load is less in sodium-depleted persons (Baldes and Smirk, 1934) and the diuresis may appear many hours after the expected time (McCance, 1936).

The effects of sodium depletion discussed so far have been mainly those which can be reasonably attributed to fall in the extracellular fluid volume, and particularly in the plasma volume. In clinical sodium depletion it is usual to find a low rather than a normal plasma sodium; this indicates that the concentration of sodium in body fluids is lowered as well as the volume of body fluid. It is not possible to decide from established clinical sodium depletion whether volume or concentration of body fluid is the more strictly preserved; but observation of the serial changes in developing experimental sodium depletion tends to vindicate the dictum of Peters and Van Slyke (1931) that the osmotic concentration of body fluids is a 'most jealously guarded constant'. In moderate sodium depletion, such as is induced by dietary sodium restriction alone, the plasma sodium remains within the normal range. McCance (1936) compared the sodium deficit with

the loss of body-weight in his sodium-depleted subjects and found that for some days the curves ran parallel, indicating that sodium concentration was being conserved by the sacrifice of extracellular fluid volume. Later, body-weight fell more slowly than body sodium, indicating that now the volume of body fluid was being kept up even at the expense of some decline in sodium concentration, with its implied fall in osmotic pressure. The effects of a fall in sodium concentration are perhaps more particularly to be observed in the next syndrome which we shall discuss, that of water intoxication; but since some of them are in fact noted in clinical sodium depletion, they may be mentioned here. Their general import is that in severe sodium depletion the loss of water is less great than that of sodium.

Cramps have been observed in diabetic coma, in heat exhaustion, and in Addison's disease (Mach, 1946); these are probably related to lowered sodium concentration rather than to lowered extracellular fluid volume, as they occur in acute sodium depletion, where the body fluids are kept at normal levels by water drinking. The profound mental changes of sodium depletion (McCance, 1936) are also unlikely to be due to circulatory disturbances, as the peripheral circulatory failure of shock or haemorrhage is not associated with similar symptoms. It is possible that some of the mental changes may be related to the retention of urea and other metabolites, the 'azotémie par manque de sel' of French authors. The rise in blood urea can mostly be attributed to the renal circulatory impairment already mentioned; but there is also evidence that urea production within the body is increased in sodium depletion, or at least in 'dehydration', for the early work did not consider the possible separate effects of water and sodium depletion. More recently, Glass (1932) in dogs, and McCance (1936) in man, have shown that sodium depletion without water depletion is associated with increased urea formation, as well as with an impaired excretion of urea. This increased breakdown may merely represent part of the adrenal response to

the stress involved in the causes of sodium depletion; but the known relationship between salt concentration and the stability of protein sols (Hardy, 1905) suggests that changes in the sodium concentration in body fluids may have a more direct part in causing protein breakdown. An interesting demonstration of the dependence of proper tissue function on a normal sodium concentration is that of Streeten (1950), who has shown that concentrations of sodium and chloride similar to those found in patients with intestinal obstruction will impair the contractility of human intestinal muscle, and may thus contribute to the ileus of late intestinal obstruction.

CLINICAL ASPECTS OF SODIUM DEPLETION WITH WATER DEPLETION

Many of the clinical feature of 'salt depletion' are implicit in what we have said of the pathogenesis of the syndrome. The pinched appearance, the dry and wrinkled skin, the parched tongue, and the lowering of intra-ocular tension are related to diminished extracellular volume; a low bloodpressure, collapsed veins, and cold limbs with some cyanosis express peripheral circulatory failure. Although the tongue is dry, thirst is rather noticeably absent in pure sodium depletion; McCance (1936) comments on this, describing a peculiar sensation, a 'loss of taste', associated with sodium depletion, but differing from true thirst, and in particular not relieved by large draughts of water. Wolf (1950) has shown that thirst is largely related to intracellular dehydration and would therefore not be expected in sodium depletion, where the loss of water is primarily extracellular. The presence of peripheral circulatory failure and the absence of thirst in sodium depletion deserve emphasis, as they are the best purely clinical guides in distinguishing predominant salt-depletion from predominant water depletion. A history of loss of saline fluids, usually by vomiting or diarrhoea, is also suggestive of predominant salt depletion.

When the clinical suspicion of sodium depletion has been

aroused, it should be supplemented by biochemical observations. The most direct of them is an estimation of the plasma sodium, which can be done quickly by using the flame photometer (Domingo and Klyne, 1949). A low plasma sodium indicates sodium depletion, provided that the total amount of body fluid is normal or reduced; this proviso excludes the syndrome of water intoxication to be described later, in which the plasma sodium is also below normal. Rarely, the plasma sodium may be normal or even high, in states of sodium depletion (Borst, 1936; Allott, 1939); the urine contains only traces of sodium. The explanation of low sodium excretion in the presence of a high plasma sodium probably lies in depression of the GFR, which diminishes the load of filtered sodium to subnormal levels, even though the plasma concentration of sodium is raised. The possibility of a normal or high plasma sodium in salt depletion should be remembered, especially in the presence of renal disease, but the general rule is that salt depletion is associated with a low plasma sodium, below 135 mEq./L.

If a flame photometer is not available, the estimation of plasma chloride and plasma bicarbonate, expressed in mEq./L., gives an approximation to the plasma sodium level. The sum of these anions is 120—130 mEq./L. normally, and values below 120 mEq./L. suggest sodium depletion. In acidosis caused by organic acids (diabetic ketosis) or by retention of sulphate or phosphate (renal failure), the sum of chloride and bicarbonate is reduced even when there is no salt depletion.

The test for chloride in the urine has been much used as an index of sodium depletion, and often a low urinary chloride does indicate sodium depletion. It must be pointed out, however, that chloride may still be present in the urine in some types of sodium depletion as in Addison's disease, in 'salt-losing nephritis', and when the sodium depletion is associated with acidosis.

There is in fact no single biochemical test which can be used as a rapid touchstone in detecting sodium depletion, and a

decision should be based on the history of fluid loss, on the clinical picture with special regard to thirst and peripheral circulatory failure, and on those biochemical data which can be quickly available. The plasma sodium, chloride and bicarbonate, the blood urea, and the urinary chloride give a fair picture of changes in electrolyte concentrations; but since they give no information on the total amount of fluid in the body, it is foolish to interpret them in isolation from the clinical history and findings. Many disturbances of sodium metabolism are associated with potassium depletion, and any comprehensive scheme of electrolyte investigation should include estimation of the plasma potassium. The haematocrit may also be of value in showing haemoconcentration, but is invalidated by previous anaemia.

General rules can not be laid down for the treatment of sodium depletion which can arise in many different ways and be associated with other electrolyte abnormalities, such as acidosis, alkalosis or potassium depletion. It can of course be said that sodium depletion will not be relieved without the establishment of a positive sodium balance; but the means by which this can be done vary with the cause of the sodium depletion, and mere provision of saline fluid may not be enough to effect it. For example, in Addison's disease hormone treatment may be necessary before a high salt intake is effective, and in diarrhoea saline infusions are less important than arrest of the diarrhoea. Although the provision of sodium in salt depletion has the limitations of any symptomatic treatment, it can be of very great value. The details of treatment scarcely come within the scope of a review of sodium metabolism, but one practical comment may be made. In attempts at quantitative replacement of a sodium deficit, the amount of sodium to be given must be obtained by assuming that the observed deficit of plasma sodium is spread over the whole body water, not just over the extracellular fluid (Peters, 1947). For example, a deficit of 20 mEq./L. in plasma sodium represents a body deficit of 700 mEq. of sodium in a 50 kg. man,

and not one merely of 200 mEq. of sodium. This is so, because of the shift of water into the cells in sodium depletion; as the plasma sodium rises during replacement, water returns to the extracellular space, and the plasma sodium is not finally restored to normal until the higher amount of sodium has been given. Water must be provided freely during active sodium replacement, to allow of re-expansion of body fluids. The magnitude of the body deficit of sodium associated with say a 10 % change in the plasma sodium level has not always been appreciated in treatment.

2) SODIUM DEPLETION WITHOUT WATER DEPLETION — 'WATER INTOXICATION'

This syndrome does not commonly arise spontaneously, as the natural consequence of sodium depletion is some degree of water depletion. The syndrome occurs only when the attempt of the body to conserve sodium concentration at the expense of body fluid volume is frustrated by a forced intake of water or by urinary suppression. This may happen as an acute phenomenon when the thirst provoked by heavy sweating is assuaged by non-saline fluids, as in miners' or stokers' cramps. It may happen more insidiously when patients with sodium depletion are given too high an intake of water or of glucose solution. It is difficult to produce water excess in normal people, for the lowering of the osmotic pressure of body fluids inhibits the pituitary anti-diuretic mechanism (Verney, 1947). The water diuresis which is so produced eliminates the abnormal water-load. This defence against water intoxication is absent in patients with anuria or profound oliguria, and even to some degree in patients after operation, who do not respond with a normal diuresis to a water load (Cooper et al., 1948). It can also be abolished artificially by injection of posterior pituitary extract, as in the water pitressin test for epilepsy (McQuarrie and Peeler, 1931). Although the low concentration of plasma sodium is the

essential feature of water intoxication and the syndrome can therefore occur with a normal total body sodium, it is more likely to arise when absolute sodium depletion has been established. There is, however, no sharp division between the effects of sodium depletion without water depletion, and those of water excess, where the body sodium is normal, but its concentration is reduced by an expansion of body water. Sodium depletion is not essential to the syndrome we are discussing, but it predisposes to it; for example, a single injection of pitressin tannate after a week on a low-sodium diet has produced mild symptoms of water intoxication, on a normal water intake. Moreover, the importance of a relative sodium lack in the pathogenesis of water intoxication is shown by the observation of Weir, Larson and Rowntree (1922) that convulsions caused by water excess are promptly inhibited by the injection of hypertonic saline, which does not of course reduce the abnormal water-load, but merely adds an equivalent load of sodium salt. Hypertonic urea does not relieve the convulsions (Harding and Harris, 1930). The most intensive studies of water intoxication were those of Rowntree (1922). Since then, the syndrome has been reported occasionally when the water intake has been forced after operation. It is only fairly recently that the importance of water excess as a danger in patients with anuria has been appreciated, by Lattimer (1945) and others; Bull et al., (1949), have described a regime for the treatment of anuria in which limitation of the water intake is stressed. Rowntree's work preceded both the methods and the custom of experimental distortion of electrolyte equilibrium in man; and widespread clinical interest in the syndrome is very recent, so that detailed studies on the metabolic effects of water intoxication in man are lacking. Weir, Larson and Rowntree (1922) produced the syndrome in dogs by giving 50 ml. of water per kg., by stomach tube. Although some of the administered water was lost by vomiting and diarrhoea, and by water diuresis, the animals were found to have dilution of the

blood, and showed restlessness, salivation, and muscle twitching in the early stages, with convulsions and coma preceding death. The distribution of the added water between extracellular and intracellular fluid was not studied. Many of the symptoms point to a heightened irritability of the central nervous system, before the onset of coma; cerebral oedema is recorded in a patient who died after rectal infusion of 9 litres of tap water, of which 6—7 L. were retained (Helwig et al., 1935). Helwig and his colleagues induced water intoxication in rabbits by proctocylsis, thus avoiding the vomiting which complicated Rowntree's observations on dogs. They found the chloride content of the brain and other organs reduced to about half the normal. The dilution of the blood associated with water-drinking after pitressin is shared by the cerebro-spinal fluid (Fremont—Smith, 1931). Expansion of the extracellular space by saline infusion does not cause convulsions, so the dilution of sodium chloride is probably the essential factor in heightening the irritability of the nervous system. The threshold of response of the brain to electrical stimulation falls with decline in the plasma sodium (Woodbury and Davenport, 1949). Although the effects of water intoxication on the nervous system tend to dominate the clinical picture, the primary disturbance which permits the syndrome to develop must be elsewhere. There is no obvious circulatory impairment, and the blood pressure may be raised; even in adrenalectomised animals, which are specially susceptible to water intoxication, the circulation is well maintained (Gaunt, 1944). Nevertheless, the renal defence against water intoxication becomes less efficient as the syndrome develops, with failure of water diuresis, and even an increase in the output of chloride (Underhill and Sellick, 1925). The cause of this impaired renal function has not been adequately studied; Boss, Birnie and Gaunt, (1950) have observed that GFR may be reduced in water intoxication in adrenalectomised rats in spite of there being no general circulatory failure. The distribution of the excess water within the body has

not been studied in man, but Eichelberger and Roma (1949) found that in dogs much of the added water was inside the cells.

Clinical aspects of water intoxication

Although the more dramatic clinical effects have been reported from time to time, water intoxication has received little attention as a possible cause of symptoms in patients convalescing from operation, or with urinary suppression. Amounts of up to 8 litres a day of water have been used in the Schemm (1942) regime for the treatment of oedema; often this produces a diuresis but this may fail, and patients are then in danger of water intoxication. The polyuria of chronic renal failure may make us forget that these patients have an inadequate diuretic response to excessive amounts of water, and too much zeal in pushing a low-salt high-fluid intake can certainly cause sodium depletion, without a corresponding depletion of water. The applied physiology of uraemia is a tangled skein, but water intoxication may well be one of the strands.

Convulsions and coma caused by water intoxication are of coutse uncommon, but anorexia, apathy and weakness are associated with early experimental water intoxication. Later, retching, nausea, and muscular twitchings become prominent. These symptoms do not form by themselves a clearly-defined syndrome, and an assessment of the clinical importance of water intoxication will depend on more careful studies of water balance and of plasma sodium concentration in patients after operation. If a significant positive water balance is found, the fluid intake should be cut down to a litre a day, and sweating encouraged by radiant-heat cradle. Convulsions caused by water intoxication respond to hypertonic saline injection.

3) SODIUM EXCESS WITH WATER EXCESS – "GENERALISED OEDEMA".

The possible causes of sodium excess in the body have already been considered, not indeed completely, but using cardiac

and renal oedema as examples of the type of process which may be involved. The prevailing view is to regard sodium retention as the primary event in the formation of generalised oedema, the accumulation of water being regarded as a secondary phenomenon. When water intake is not restricted, a rise in the osmotic pressure of body fluids can be prevented by retaining water to a degree corresponding to the already established sodium excess. The gain in weight and the appearance of clinical oedema are unequivocal signs that such a retention of water has in fact occurred, and oliguria is present when oedema is increasing, while loss of oedema is necessarily associated with a diuresis. Any tendency towards increase in the osmotic pressure of body fluid stimulates production of the antidiuretic hormone of the posterior pituitary, and of the mechanisms at present known this seems the most likely one to be responsible for the water retention which generally accompanies sodium retention.

The excess of body fluid so produced is accommodated in the extracellular compartment, and the cells do not contain an excess of water; there may even be cellular dehydration, when the water intake has been restricted to such an extent that the plasma sodium is higher than normal. This may be clinically apparent, when patients with anasarca show a dry tongue and complain of severe thirst; these are clear signs that restriction of water, as opposed to salt, intake has been excessive. The distribution of fluid within the extracellular compartment, i.e. between plasma and interstitial fluid, is governed by the balance between the colloid osmotic pressure of plasma protein and the hydrostatic pressure within the capillaries. In the oedema caused by plasmapharesis, fluid accumulates in the interstitial spaces, and the plasma volume itself is reduced; this loss of plasma volume is a powerful stimulus to sodium retention, and may act through the adrenals (Peters, 1950). On the other hand, when oedema is produced by excessive infusion of sodium salts, an increased plasma volume is primary, and fluid escapes into the tissues only

as the plasma proteins are reduced in concentration by the infusion; in health, this redistribution of extracellular fluid occurs very rapidly, as shown by the fact that an infusion of 200 ml. of 5 % saline given in 20 minutes is distributed in that time over the whole extracellular space. This rapidity of equilibrium between plasma and interstitial fluid is scarcely surprising, in view of the enormous interface provided by the capillary bed; it largely invalidates arguments as to the cause of oedema based on measurements of plasma volume, since primary renal sodium retention and sodium retention secondary to capillary leakage may give much the same end-result — an expansion both of plasma and of interstitial fluid volume — when adaptive retention of sodium by the kidneys has been completed. In fact, the plasma volume in oedematous states is inaccurately determined by dye methods, as protein leakage in the viscera may give falsely high values; also, even accurate determinations based on labelled red cells are difficult to interpret, as the plasma volume seems to depend much more on the mass of total circulating protein than on changes in sodium metabolism. Observations made when oedema is being rapidly formed, as in early Type I nephritis, are of some value in indicating a primary sodium retention (Roscoe, 1950), but in established cardiac oedema the estimation of plasma volume has not been helpful in defining the mechanism of oedema production (Peters, 1948).

Although many of the causes of clinical oedema, including cardiac failure, are associated with measurable impairment of renal function, oedema in itself does not cause a 'functional renal failure', unless perhaps when the kidneys are themselves oedematous. Rise in renal vein pressure leads experimentally to albuminuria, and to suppression of urine flow (Winton, 1931) but the clinical importance of renal oedema has yet to be demonstrated, and the available studies of renal function in oedematous states suggest that a defect of blood-flow to the kidneys is more important than any back-pressure effects upon

them. Urea retention is indeed common in patients with the oedema of cardiac failure, but is most probably related to depression of glomerular filtration rate. Tubular reabsorption of sodium is active in those types of oedema where it has been studied.

Not all types of oedema can be explained in terms of abnormal sodium metabolism. An obvious example in inflammatory oedema, where the capillaries become more permeable, and the oedema fluid contains both cells and protein. It is well known that excessive infusion of normal saline may cause moist sounds at the lung bases, and pulmonary oedema is found at autopsy. It is possible to explain systemic oedema after saline infusion by dilution of plasma proteins, for in the systemic capillaries hydrostatic and colloid osmotic pressure are fairly closely balanced. The pulmonary circulation, however, is a low-pressure system, and the colloid osmotic pressure of plasma is very considerably in excess of the pressure normally found in the pulmonary capillaries (Cournand, 1950). The explanation of pulmonary oedema after massive saline infusion must lie either in acute left ventricular failure, for which there is little evidence, or in a sudden increase in the permeability of the pulmonary capillaries to protein. The high protein content of pulmonary oedema fluid supports the second explanation, but we do not know why a sudden expansion of the blood volume with saline fluid should affect the permeability of the pulmonary capillaries.

CLINICAL ASPECTS OF OEDEMA

Although sodium retention is not certainly established as the prepotent cause of generalised oedema, the modern therapy of oedema is largely based on attempts to eliminate sodium, and to restrict sodium intake. On the level of symptomatic relief, such measure are often rewarded with considerable therapeutic success. Either mercurial diuretics or sulphonamides (Schwartz, 1949) can be used to inhibit part of the tubular reabsorption of sodium. An increased excretion of sodium has been noted after

mercury administration, even when the urine volume is not increased (Sollmann, 1948). Restriction of sodium in the diet is also accepted as part of the treatment of oedema. It is possible to devise special diets, like the rice diet of Kempner (1945), which contain less than 0.2 g. of sodium per day; but these are not well tolerated by most patients. An ordinary 'low-salt' diet has about 3 g. of salt per day, and this can be brought down to less than 1 g. of salt a day by using bread baked without salt. In patients with nascent oedema, the use of a diet of this type will reduce the frequency of mercurial injections needed to prevent increase of oedema (Reid and Hughes, 1949). Severely restricted diets tend to monotony, and sceptics may feel constrained to test the faithfulness of their patients by frequent estimations of the chloride content of the urine. An alternative approach in the future may be to give an ordinary diet, without added salt, and to give with it about 100 g./day, in divided doses, of an effective cation exchange resin (Dock and Franks, 1950). The sodium in the food is exchanged for hydrogen ions, and these tend to cause some acidosis; potassium loss is also a possible danger, as the affinity of most resins for potassium is greater than for sodium. Further metabolic studies are obviously needed on exchange resins before they are regarded as suitable agents for general treatment of oedema. It sometimes happens that patients are resistant to mercurial diuretics in the sense that no sodium diuresis follows their use; and the urinary output of sodium is so small that dietary restriction of sodium is quite ineffective in ridding them of oedema. There is then a place for direct removal of oedema fluid by modified Southey's tubes, under penicillin cover to prevent the infection which has brought this form of treatment into disfavour. Large amounts of fluid can be removed in this way, and sometimes a diuresis has been observed after oedema has been lessened by direct means (Fiese and Thayer, 1950).

While sodium restriction is mandatory in patients with oedema,

water need not be greatly restricted, and thirst should be satisfied. Schemm (1942) has even claimed that a forced intake of non-saline fluid can promote loss of oedema; but the expected diuresis does not always follow a high water load, and this treatment is not generally adopted. A water intake enough to relieve thirst is desirable, and will prevent the occurrence of cellular dehydration which may complicate oedema in patients whose water intake has been insufficient.

4) SODIUM EXCESS WITHOUT WATER EXCESS

Like the sodium depletion of water intoxication, the sodium excess of this fourth syndrome is not necessarily absolute, but may be relative to the water content of the body. It corresponds to the 'water depletion' of Marriott, and has as its essential biochemical feature an increase in the concentration of plasma sodium. It may arise in primary sodium excess, when the usual effect of expansion of the extracellular fluid is prevented by an inadequate intake of water; or loss of water may produce the syndrome, and sodium excess may only appear when the capacity of the kidneys to excrete sodium is impaired by limitation of the amount of water available for this purpose. The syndrome may even be present in all essentials when the sodium content of the body is lower than normal, provided that the water content of the body is reduced to an even greater extent; this is seen in subjects who are deprived of water when on a low-sodium diet. On normal diets, however, water deprivation is associated with a positive sodium balance, so that the absolute amount of sodium in the body is increased as well as the sodium concentration in plasma (Black, McCance and Young, 1944).

In the discussion on sodium depletion with associated water depletion, it was pointed out that the burden of fluid loss fell on the extracellular fluid compartment, with an early depletion of circulating plasma volume. By contrast, the fluid loss of a primary water deficiency is spread rather uniformly over the

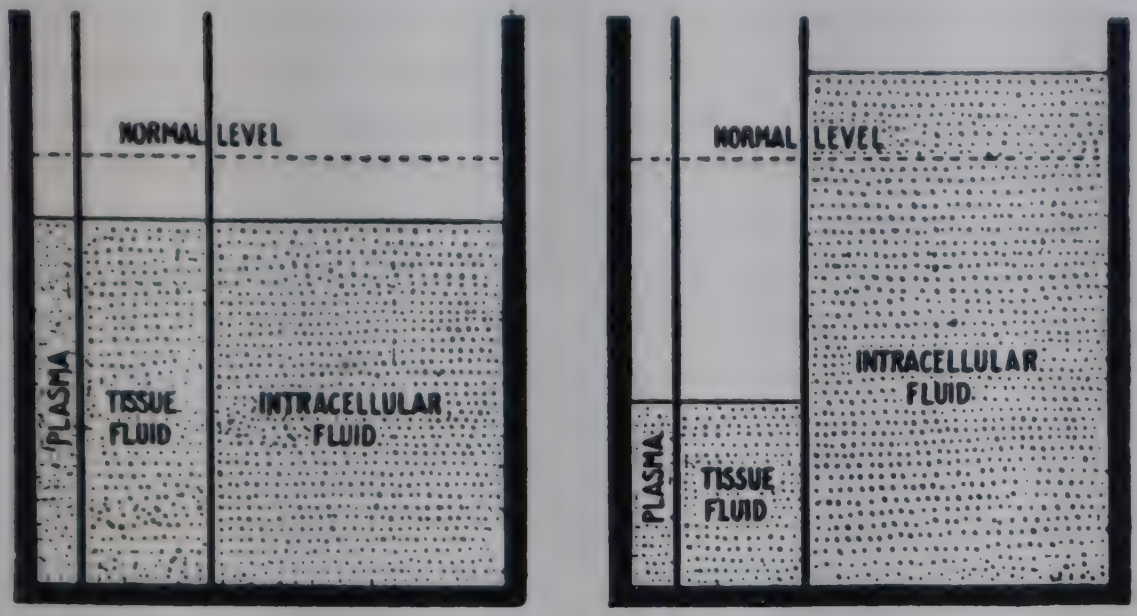

Fig. 4. Changes in the volume of Fluid in different body-fluid compartments in (A) primary water depletion, and, (B) primary salt depletion (modified from Marriott, 1950).

whole mass of body fluid; figure 4 shows the relative changes in the amount of fluid in the various compartments in these two states. Although water is lost initially from the plasma through the skin and lungs, the rise in osmotic pressure of plasma promotes the passage of water out of the cells. The relative losses of sodium and potassium give some measure of the contribution made respectively by extracellular and intracellular fluid; and Black, McCance and Young (1944) found that the fluid loss was derived from extracellular and intracellular fluids in a proportion corresponding to the relative size of these two compartments. Loss of intracellular fluid was clearly shown by a loss of potassium greatly in excess of the amount of potassium accounted for by protein breakdown. An increased production of urea was found, showing that some increased protein breakdown had in fact occurred. These results, obtained in man, are in essential agreement with those of Elkinton and Taffel (1942) in dogs. Losses of potassium similar to those seen in experimental water deprivation can be seen when excessive amounts of

saline fluid are given (Wallace 1948); and this mechanism may play some part in the potassium deficiency which has been observed after gastro-enteritis and diabetic coma (Darrow, 1950).

The loss of water from the cells is also reflected in a cardinal symptom of sodium excess, severe thirst. Wolf (1950) has undertaken an experimental analysis of this symptom in dogs and man, and his results show that thirst depends on the osmotic concentration of body fluids, and not on their absolute amount. Thirst is present when the body fluids are expanded by hypertonic saline injection, and absent when the sodium concentration of extracellular fluid is low, even although the total body fluid is reduced in amount. Thirst in fact seems to be complementary to pituitary antidiuretic activity in maintaining the osmotic pressure of body fluids within limits. Rise in osmotic pressure promotes water drinking and depresses water elimination, while fall in osmotic pressure has the opposite effects; both mechanisms seem insensitive to the volume of body fluid, as opposed to its concentration.

In contrast with salt depletion, the circulating blood volume in water depletion is comparatively well maintained. The blood-pressure remains normal, and peripheral circulatory failure is absent in the early stages, though it may appear when the total body fluid is grossly depleted. For any given weight loss, the circulation in water depletion is much more efficient than in salt depletion. The kidneys share the benefits of this relatively good circulation; Black et al. (1942) found that the renal blood-flow and GFR were very little reduced in water depletion in human subjects. These results have recently been challenged by Kenney (1949), who found significant depression of renal blood flow in water depletion. A possible explanation of this discrepancy may be in the fact that Kenney's subjects were not on a fixed protein intake. Water depletion is associated with anorexia, and a low protein diet depresses renal blood-flow. Renal function in water depletion has been studied more fully by McCance et al. (1944).

They found that a urine of high concentration was formed, but that the limitation of water available for urine formation prevented the complete excretion of urea and of electrolytes, so that both the blood urea and the plasma sodium increased. The kidneys are presumably acting under pituitary antidiuretic influence, for the osmotic pressure of plasma is above normal and an antidiuretic material has been isolated from the urine of water-depleted rats (Gilman and Goodman, 1937).

Clinical aspects of water depletion

The presence of thirst and the absence of signs of peripheral circulatory failure suggest that water depletion predominates over salt depletion. A raised plasma sodium is biochemical evidence of the same thing, and may be found not only when excessive amounts of saline have been given, but also when water losses have occurred without replacement. As already mentioned, a raised plasma sodium does not positively exclude sodium deficit in the body; it shows that water deficit is still greater, and should have priority in treatment. A low 24-hour urine volume, especially if it be associated with a high specific gravity, and high concentration of sodium, chloride and urea, is a sign that water intake is inadequate. A free intake of water by mouth is the ideal treatment for water depletion, but 5 % glucose, without saline, by vein may have to be used in comatose or apathetic patients, or in those with vomiting. The difficulty in water depletion is one of recognition rather than of treatment, and it is here that Marriott's work has been of the greatest value in forcing the distinction between water and salt depletion into the day to day thoughts of the practising clinician.

These four syndromes just described cover most of the common derangements of sodium metabolism. Two of them (syndromes 1 and 3) involve predominantly change in the amount of body fluid, and the changes in sodium and water are in the same direction. In the other two syndromes, the sodium and

water content of the body has changed in the opposite way, so that the osmotic concentration of body fluid is distorted more significantly than its absolute amount. It is perhaps necessary to reiterate that the dissociation between amount and concentration which we have made in describing these syndromes is to some extent an analytical fiction; descriptions of the pure syndromes are very largely based on experimental work, and the clinical problems actually met with are complicated not only by the occurrence of combinations of the pure experimental syndromes, but also by biochemical distortions not primarily related to sodium metabolism, such as acidosis and alkalosis.

While the relationships between sodium and water metabolism have been studied for some decades, and a considerable body of knowledge has accumulated, the effect on sodium metabolism of changes in the metabolism of other electrolytes, notably potassium and the anions chloride and bicarbonate, has been studied intensively only within the past few years. The close connection between sodium, potasium, and acid-base balance is well seen in some patients with Cushing's syndrome, who are in alkalosis, with raised plasma sodium and low plasma chloride; this alkalosis resists therapy with acidifying salts, but disappears when potassium is given in adequate amount (Willson, Power and Kepler, 1937). This type of syndrome is inaccessible to the conventional methods of study of electrolyte metabolism, which have been built up largely in relation to extracellular fluid; for the primary changes seem to lie within the cells. The relationships involved have been reviewed in some detail by Elkinton et al. (1948), and Darrow (1950), and a good general account of the problem is given by Newburgh (1950). We shall not attempt to summarise these reviews here, for the primary distortion seems to be in potassium metabolism or in the acid-base balance, and not in sodium metabolism, and we have already discussed the more relevant aspects of change in intracellular sodium.

We shall also omit any detailed discussion of the relationship

between sodium metabolism and hypertension, because nothing is known of the mechanism whereby the sodium content of the diet influences the blood-pressure level. It is indeed established that a diet very low in sodium will lower the blood-pressure in many hypertensive patients, though seldom to normal levels (Kempner, 1945: M.R.C. Report, 1950). The blood pressure may fall in the absence of any demonstrable fall in plasma volume. It is also known that a high-sodium diet potentiates the hypertension which can be produced by massive doses of DCA (Selye and Hall, 1943); and that hypertensive patients excrete more sodium than normal people when put on a low-sodium diet (Perera and Blood, 1946). The explanation of these observations is, however, completely elusive in the present state of our knowledge of sodium metabolism and hypertension. Current speculations have been summarised by Chapman and Gibbons (1950).

At the close of this review of sodium metabolism, we may allow ourselves a paragraph or two of speculation on the present status of the subject. On the practical level, the study of sodium metabolism has justified itself in the more effective treatment of such common syndromes as diabetic coma, pyloric stenosis, severe diarrhoea, and generalised oedema. When sodium metabolism is considered as a facet of pure science, however, the medical worker in this field finds himself frustrated by relative or absolute ignorance of the physicochemical principles which obviously govern the behaviour of electrolytes in body fluids. A large number of 'brute facts' relating to sodium metabolism has accumulated, but synthesis of these into a scheme which would satisfy the physical chemist has scarcely begun. As in many other fields, however, the biologist cannot just content himself with making observations, and leaving their interpretation to the non-medical scientist; for Adolph's distinction between the 'observational' and the 'interpretative' level of science is largely vitiated by the fact that significant observations are not only followed, but also preceded by some degree of inter-

pretation. Otherwise, we are left with a 'chaos of clear ideas', to apply Desmond McCarthy's description of Voltaire's philosophy to a rather different field. Future advances in our knowledge of sodium metabolism seem to lie in the provision of a framework wherein clinician, experimentalist, and pure scientist can collaborate on equal terms, and learn each other's language.

It would be unfortunate if anything said in this review should suggest that the subject of sodium metabolism in any of its aspects is a closed one. The review has been largely based on the widely-held assumption that osmotic equilibrium prevails throughout the body, and so far as we can tell this assumption is pragmatically correct, in that treatment carried out to restore a 'normal' osmotic pressure in extracellular fluid does benefit the patient. However, Robinson (1950) has shown most convincingly that the osmotic pressure within cells may be much higher than that outside, and that their water content is kept low by an active extrusion of water, whose continuance depends on aerobic cell metabolism. When this is depressed by anoxia, water enters the cells. On this basis, an increase in plasma sodium might not imply an increase in the amount of osmotically active material within the body, but might represent merely a transfer of water into cells through breakdown of the water-extrusion mechanism. Welt et al. (1950) found that the plasma sodium rose after convulsions had been induced electrically, and they explain their results as representing an induced 'cellular hyperosmolarity'; but defect in water extrusion could account for the same change. This example may show that even apparently established principles of sodium metabolism may have to be revised from time to time. The need for such revision should be tacitly remembered by all scientific workers in this, as in other fields. If this dynamic attitude to the problem deprives us of the solace of fixed principles, it is at least appropriate to the study of sodium, which builds reality out of process in our extracellular fluid.

REFERENCES

Adolph, E. F., (1943). Physiological Regulations.

Baldes, E. J. and Smirk, F. H., (1934). *J. Physiol.*, **82,** 62.

Bartter, F. C., Fourman, P., Albright, F., Forbes, A. P., Jefferies, W. M., Griswold, G., Dempsey, E., Bryant., D., and Carroll, E. (1950). *J. Clin. Invest*, **29,** 950.

Berliner, R. W., (1950). *Amer. J. Med.*, **9,** 541.

Black, D. A. K., Platt, R., and Stanbury, S. W., (1950). *Clin. Sci.*, **9,** 205.

Black, D. A. K., McCance, R. A., and Young, W. F. (1944). *J. Physiol.*, **102,** 406.

Black, D. A. K., McCance, R. A., aud Young, W. F., (1942). *Nature* **150,** 461.

Blake, W. D., Wegria, R., Keating, R. P., and Ward, H. P., (1949). *Amer. J. Physiol.*, **157,** 1.

Boss, W. R., Birnie, J. H., and Gaunt, R., (1950). *Endocrinology*, **46,** 307.

Brod, J., and Fejfar, Z., (1950). *Quart. J. Med.*, **19,** 187.

Brodsky, W. A., Rapoport, S., and West, C. D., (1950). *J. Clin. Invest.*, **29,** 1021.

Bull, G. M., Joekes, A. M., and Lowe, K. G. (1949). *Lancet*, 1949, **2,** 229.

Cardozo, E. L., (1946), *Acta med. Scand.*, **125,** 333.

Chapman, C. B., and Gibbons, T. B., (1950). *Medicine*, **29,** 29.

Conn, J. W., (1949), *Arch. intern. Med.*, **83,** 416.

Conway, E. J., (1945), *Biol. Rev.*, **20,** 56.

Conway, E. J., (1947), *Irish J. Med. Sci.*, 1947, 593 and 654.

Cooper, D. R., Iob, V., and Coller, F. A., (1948). *Ann. Surg.*, **129**, 1.

Cournand, A., (1950). *Circulation*, **2,** 641.

Darrow, D. C., (1945). *New Eng. J. Med.*, **233,** 91.

Darrow, D. C., and Pratt, E. L., (1950). *J. Amer. Med. Ass.*, **143,** 432.

Darrow, D. C. (1950). *New Eng. J. Med.*, **242,** 978, 1014.

Darrow, D. C., and Yannet, H., (1935). *J. Clin. Invest.*, **14,** 266.
Deane, H. W., Shaw, J. H., and Greep, R. O., (1948). *Endocrinol.*, **43,** 133.
Dill, D. B., Jones, B. F., Edwards, H. T., and Oberg, S. A., (1933), *J. Biol. Chem.*, **100,** 755.
Dock, W., and Frank, N. R., (1950), *Amer. Heart J.*, **40,** 638.
Domingo, W. R., and Klyne, W. (1949). *Biochem. J.*, **45,** 400.
Duggan, J. J., and Pitts, R. F. (1950). *J. Clin. Invest.*, **29,** 365.
Eggleton, M. G., and Smith, I. G. (1946). *J. Physiol.*, **104,** 435.
Eichelberger, L., and Roma, R. (1949). *Amer. J. Physiol.*, **159,** 57.
Eliel, L. P., Pearson, O. H., and Rawson, R. W. (1950). *New Eng. J. Med.*, **243,** 471.
Elkinton, J. R., and Taffel, M. (1942). *J. Clin. Invest.*, **21,** 787.
Elkinton, J. R., Winkler, A. W., and Danowski, T. S. (1948). *J. Clin. Invest.*, **27,** 74.
Ellis, A. (1942). *Lancet*, 1942, **1,** 1.
Fiese, M. J., and Thayer, J. M. (1950). *Arch. Int. Med.*, **85,** 132.
Findlay, A. (1942). Introduction to Physical Chemistry.
Fishberg, A. M. (1940). Heart Failure, 2nd. Ed.
Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G. (1948). *J. Clin. Encrocrinol.*, **8,** 15.
Fremont-Smith, F. (1931). *Brain*, **54,** 303.
Gamble, J. L. (1947). Chemical anatomy, physiology and pathology of extracellulair fluid.
Gaunt, R. (1944). *Endocrinology*, **34,** 400.
Gilman, A., and Goodman, L. (1937). *J. Physiol.*, **90,** 113.
Glass, J. (1932). *Z. ges. exp. Med.*, **82,** 776.
Grant, R. T., and Reeve, E. B. (1941). *Brit. Med. J.*, 1941, **2,** 293.
Harding, V. J., and Harris, L. J. (1930). *Trans. Roy. Soc. Canada*, Sect V, **24,** 101.
Hardy, J. D. (1950). *Ann. Surg.*, **132,** 189.
Hardy, W. B. (1905—06). *J. Physiol.*, **33,** 251.
Helwig, F. C., Schutz, C. B., and Curry, D. E. (1935). *J. Amer. Med. Ass.*, **104,** 1569.
Hodgkin, A. L., and Katz, B. (1949). *J. Physiol.* **108,** 37.
Kriss, J. P., and Futcher, P. H. (1949). *J. Clin. Endocrinol.*, **9,** 13.
Kempner, W. (1945). *North Carolina Med. J.*, **6,** 61.
Kenney, R. A. (1949). *Acta. Med. Scand.*, **135,** 172.
Kruhoffer, P. (1950). Studies on water-electrolyte excretion and glomerular activity in the mammalian kidney.
Ladell, W. S. S., Waterlow, J. C., and Hudson, M. F. (1944). *Lancet*, **2,** 491.

Lattimer, J. K. (1945). *J. Urol.*, **54,** 312.
Lauson, H. D., Bradley, S. E., and Cournand, A. (1944). *J. Clin. Invest.*, **23,** 381.
Leaf, A., and Couter, W. T. (1949). *J. Clin. Invest.*, **28,** 1067.
Ljungberg, E. (1947). *Acta med. Scand.*, (Supp.), **186.**
Luetscher, J. A., Hall, A. D., and Kremer, V. L. (1950). *J. Clin. Invest.*, **29,** 896.
Macallum, A. B. (1926). *Physiol. Rev.*, **6,** 316.
McCance, R. A. (1948). *Physiol. Rev.*, **28,** 331.
McCance, R. A. (1936). *Lancet*, 1936, **1,** 823.
McCance, R. A., Young, W. F., and Black, D. A. K. (1944). *J. Physiol.*, **102,** 415.
McQuarrie, J., Johnson, R. M., and Ziegler, M. R. (1937). *Endocrinol.*, **21,** 762.
McQuarrie, I., and Peeler, D. B. (1931). *J. Clin. Invest.*, **10,** 915.
Mach, R. S. (1946). Les troubles du metabolisme du sel et de l'eau.
Marriot, H. L. (1950). 'Water and Salt Depletion'.
Merrill, A. J. (1946). *J. Clin. Invest.*, **25,** 389.
Mokotoff, R., Ross, G., and Leiter, L. (1949). *J. Clin. Invest.*, **27,** 1.
Moore, F. D. (1949). *J. Amer. Med. Ass.*, **141,** 646.
M. R. C. Report (1950). *Lancet*, 1950, **2,** 509.
Mudge, G. H., and Vislocky, K. (1949). *J. Clin. Invest.*, **28,** 482.
Newburgh, L. H. (1950). Significance of the body fluids in clinical medicine.
Oliver, J. (1945). *Harvey Lect.*, **40,** 102.
Oliver, J. (1948). *J. Mt. Sinai Hosp.*, **15,** 175.
Oliver, J. (1950). *Amer. J. Med.*, **9,** 88.
Orent-Keiles, E., Robinson, A., and McCollum, E. V. (1937). *Amer. J. Physiol.*, **119,** 651.
Orloff, J., Welt, L. G., and Stowe, L. (1950). *J. Clin. Invest.*, **29,** 770.
Perera, G. A., and Blood, D. W. (1946). *Amer. J. Med.*, **1,** 602.
Peters, J. P. (1948). *New Eng. J. Med.*, **239,** 353.
Peters, J. P. (1950). *J. Mt. Sinai Hosp.*, **17,** 159.
Peters, J. P., and Van Slyke, D. D. (1931). Quantitative Clinical Chemistry.
Peters, J. P. (1947). In Duncan, 'Diseases of Metabolism', 1947.
Pitts, R. F. (1948). *Fed. Proc.*, **7,** 418.
Platt, R. (1948). *Lancet*, 1948, **1,** 23.
Reid, H. A., and Hughes, W. (1949). *Lancet*, 1949, **1**, 593.
Ringer, S. (1883). *J. Physiol.*, **4,** 29.
Robinson, J. R. (1950). *Proc. Roy. Soc.* (B), **137,** 378.

Roscoe, M. H. (1950). *Quart. J. Med.*, **19,** 161.
Rowntree, L. G. (1922). *Physiol. Rev.*, **2,** 116.
Schemm, F. R. (1942). *Ann. intern. Med.*, **17,** 952.
Schroeder, H. A. (1949). *J. Amer. Med. Ass.*, **141,** 117.
Schroeder, H. A. (1950). *Circulation*, **1,** 481.
Schwartz, I. L., Schachter, D., and Freinkel, N. (1949). *J. Clin. Invest.*, **28,** 1117.
Schwartz, W. B. (1949). *New Eng. J. Med.*, **240,** 173.
Selye, H., and Hall, C. E. (1943). *Arch. Path.*, **36,** 19.
Shannon, J. A. (1942). *J. Exp. Med.*, **76,** 371.
Shohl, A. T. (1939). Mineral Metabolism.
Sirota, J.H., Baldwin, D.S., and Villarreal, H. (1950). *J. Clin. Invest.*, **29,** 187.
Smith, H. W. (1950a). *Proc. XVIII Internat. Physiol. Cong.*, p. 50.
Smith, H. W. (1947). *Bull. N. Y. Acad. Med.*, **23,** 177.
Smith, H. W. (1950b). *Amer. J. Med.*, **9,** 216.
Snyder, R., and Katzenelbogen, S. (1942). *J. Biol. Chem.*, **143,** 223.
Soffer, L. J. (1948). Diseases of the Adrenals, 2nd. Ed.
Sollmann, T. (1948). A Manual of Pharmacology.
Stanbury, S. W. (1950). Communication to Medical Research Society.
Starling, E. H. (1909). The Fluids of the Body.
Streeten, D. H. P. (1950). *Surg. Gynec., Obstet.*, **91,** 421.
Taggart, J. V., and Forster, R. P. (1950). *Amer. J. Physiol.*, **161,** 167.
Thorn, G. W., Koepf, G. F. and Clinton, M. (1944). *New Eng. J. Med.*, **231,** 76.
Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., and Prichard, M. M. L. (1947). Studies of the Renal Circulation.
Underhill, F. P., and Sallick, M. A. (1925). *J. Biol. Chem.*, **63,** 61.
Ussing, H. H. (1949). *Physiol. Rev.*, **29,** 127.
Van Slyke, D. D. (1926). Factors affecting the distribution of electrolytes, water, and gases in the animal body.
Verney, E. B. (1947). *Proc. Roy. Soc. B.*, **135,** 25.
Visscher, M. B., Fletcher, E. S., Carr, C. W., Gregor, H. P., Bushey, M. S., and Barker, D. E. (1944). *Amer. J. Physiol.*, **142,** 550.
Walker, A. M., Bott, P. A., Oliver, J., and MacDowell, M. C. (1941). *Amer. J. Physiol.*, **134,** 580.
Wallace, W. M. (1948). *J. Clin. Invest.*, **27,** 560.
Warren, J. V., and Stead, E. A. (1944). *Arch. intern. Med.*, **73,** 138.
Weir, J. F., Larson, E. E., and Rowntree, L. G. (1922). *Arch. intern. Med.*, **29,** 306.
Welt, L. G., Orloff, J., Kydd, D. M., and Oltman, J. E. (1950). *J. Clin. Invest.*, **29,** 935.

Wesson, L. G., Anslow, W. P., and Smith, H. W. (1948). *Bull. N. Y. Acad. Med.*, **24,** 586.
Wesson, L. G., and Anslow, W. P. (1948). *Amer. J. Physiol.*, **153,** 465.
Weston, R. E., Hellman, L., Escher, D. J. W., Edelman, I. S., Grossman, J., and Leiter, L. (1950). *J. Clin. Invest.* **29,** 639.
Willson, D. M., Power, M. H., and Kepler, E. J. (1937). *J. Clin. Invest.*, **19,** 701.
Wilson, J. R., Harrison, C. R. (1950). *J. Clin. Invest.*, **29,** 251.
Winton, F. R. (1937). *Physiol. Rev.*, **17,** 408.
Winton, F. R. (1931). *J. Physiol.*, **72,** 49.
Wolf, A. V. (1950). *Amer. J. Physiol.*, **161,** 75.
Woodbury, D. M., Cheng, C., Sayers, G., and Goodman, L. S. (1950). *Amer. J. Physiol.*, **160,** 217.
Woodbury, D. M., and Davenport, V. D. (1949). *Amer. J. Physiol.*, **157,** 234.
Zweifach, B. W., and Kossmann, C. E. (1937). *Amer. J. Physiol.*, **120,** 23.

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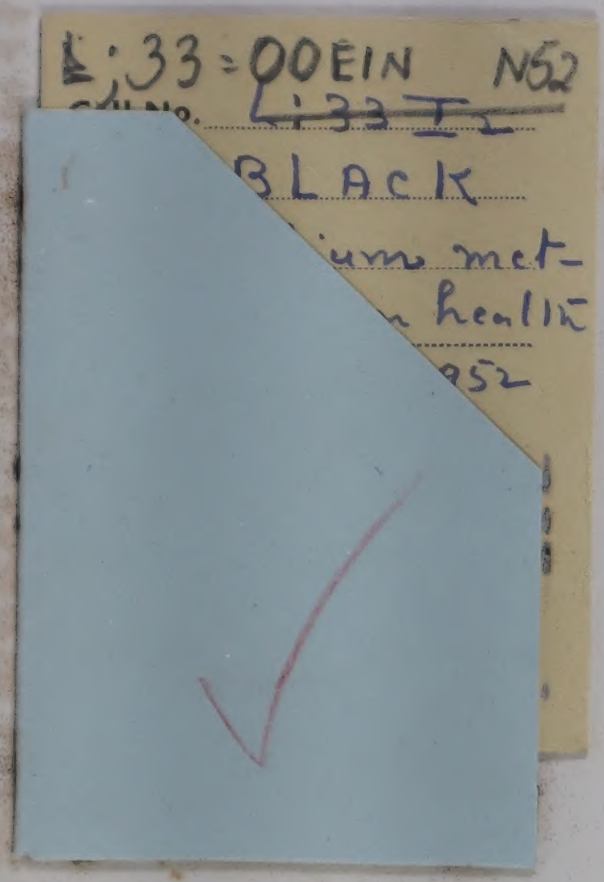
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